Anesthesiology
1997; 86:836–47

Bispectral Analysis Measures Sedation and Memory Effects of Propofol, Midazolam, Isoflurane, and Alfentanil in Healthy Volunteers

Peter S. Glass, M.D., Marc Bloom, M.D., Ph.D.,† Lee Kearse, M.D., Ph.D.,‡ Carl Rosow, M.D., Ph.D.,‡ Peter Sebel, M.B., B.S., Ph.D., F.F.A.R.S.C.I.,§ Paul Manberg, Ph.D.‖*

Background: **The bispectral index (BIS), a value derived from the electroencephalograph (EEG), has been proposed as a measure of anesthetic effect. To establish its utility for this purpose, it is important to determine the relation among BIS, measured drug concentration, and increasing levels of sedation. This study was designed to evaluate this relation for four commonly used anesthetic drugs: propofol, midazolam, isoflurane, and alfentanil.**

Methods: **Seventy-two consenting volunteers were studied at four institutions. Volunteers were given either isoflurane, propofol, midazolam, or alfentanil. Each volunteer was administered a dose-ranging sequence of one of the study drugs to achieve predetermined target concentrations. A frontal montage was used for continuous recording of the EEG. At each pseudo–steady-state drug concentration, a BIS score was recorded, the participant was shown either a picture or given a word to recall, an arterial blood sample was obtained for subsequent analysis of drug concentration, and the participant was evaluated for level of sedation as determined by the responsiveness portion of the observer's assessment of the alertness/sedation scale (OAAS). An OAAS score of 2 or less was considered unconscious. The BIS (version 2.5) score was recorded in real-time and the BIS (version 3.0) was subsequently derived off-line from the recorded raw EEG data. The relation among BIS, measured drug concentration, responsiveness score, and presence or absence of recall was determined by linear and logistic regression for both the individual drugs and, when appropriate, for the pooled results. The prediction probability was also calculated.**

Results: **The BIS score ($r = 0.883$) correlated significantly better than the measured propofol concentration ($r = -0.778$; $P < 0.05$) with the responsiveness score. The BIS provided as effective correlation with responsiveness score of the OAAS as did the measured concentration for midazolam and isoflurane. None of the volunteers given alfentanil lost consciousness and thus were excluded from the pooled analysis. The pooled BIS values at which 50% and 95% of participants were unconscious were 67 and 50, respectively. The prediction probability values for BIS ranged from 0.885–0.976, indicating a very high predictive performance for correctly indicating probability of loss of consciousness.**

Conclusions: **The BIS both correlated well with the level of responsiveness and provided an excellent prediction of the loss of consciousness. These results imply that BIS may be a valuable monitor of the level of sedation and loss of consciousness for propofol, midazolam, and isoflurane. (Key words: Anesthetics, volatile: isoflurane. Anesthetics, intravenous: propofol; midazolam; alfentanil. Electroencephalogram. Bispectral analysis.**

MEASURING the depth of general anesthesia has been an enigma ever since drugs were introduced that can render patients unconscious. The first attempts at evaluating depth of anesthesia used clinical signs such as those described by Snow[1,2] and subsequently by Guedel.[3] With the introduction of newer anesthetic compounds and the use of multiple drugs to provide the anesthetic state, these clinical signs no longer provide a reliable guide to determine the depth of anesthesia. As a result, several neurophysiologic monitors have been introduced in an attempt to provide a measure of the anesthetic state. The most widely evaluated neurophysiologic tool used to assess depth of anesthesia has been the electroencephalogram (EEG). Can the EEG be used

* Associate Professor, Department of Anesthesiology, Duke University, Durham, North Carolina.

† Department of Anesthesiology, University of Pittsburgh, Pittsburgh, Pennsylvania.

‡ Associate Professor, Department of Anesthesiology, Massachusetts General Hospital, Harvard University, Boston, Massachusetts.

§ Professor, Department of Anesthesiology, Emory University, Atlanta, Georgia.

‖ Vice President, Clinical and Regulatory Affairs, Aspect Medical Systems, Natick, Massachusetts.

Submitted for publication March 28, 1996. Accepted for publication January 2, 1997. Presented in part at the October 1995 American Society of Anesthesiologists meeting, Atlanta, Georgia. Supported in part by a grant from Aspect Medical Systems. Drs. Glass, Bloom, Kearse, Rosow, and Sebel received grant support and consulting fees from Aspect Medical Systems.

Address reprint requests to Dr. Glass: Department of Anesthesia, Duke University Medical Center, P.O. Box 3094, Durham, North Carolina 27710. Address electronic mail to: glass003@mc.duke.edu

to measure depth of anesthesia? Despite extensive research, the answer to this basic query is still unclear. In a recent review of this subject, Stanski[4] suggested that progress in answering this question has been hindered by several factors, including (1) lack of understanding of the effects of interactions of anesthetic drugs on the EEG, (2) inability to choose the most appropriate EEG parameters, and (3) lack of a gold standard of clinical drug effect for comparison. To overcome these limitations, it was recommended that use of the EEG as an anesthetic monitor will require correlation of anesthetic drug concentrations, EEG parameters, and clinical measures of depth of anesthesia first for individual anesthetic drugs and then for combinations of anesthetic drugs.

In addition, the unifying concept of what constitutes anesthesia is still evolving. Two recent editorials by Prys-Roberts[5] and Kissin[6] discuss the complex nature of how the depth of anesthesia can be defined. From these editorials, it appears that there are at least two components to the anesthetic state. The first is loss of consciousness and recall, implying inability to respond to or recall a non-noxious stimulus (*e.g.*, calling out one's name). The second component is the obtundation of reflex responses to a noxious stimulus. The ablation of reflex responses has been shown to occur below the level of the cortex and thus may be unrelated to the state of consciousness.[7,8] This concept of anesthesia is supported by several recent studies on the reduction of minimum alveolar concentrations of volatile anesthetics,[9] or propofol,[10] by opioids. In these studies, a very small amount of opioid markedly reduced the minimum alveolar concentration of isoflurane, yet an opioid alone, even at extremely high concentrations, could not prevent movement at skin incision. At these high opioid concentrations, a minimum concentration of volatile anesthetic or propofol was required to provide the anesthetic state as defined by lack of movement to skin incision. Thus the anesthetic state was provided by propofol or the volatile anesthetic reaching a sufficient concentration for loss of consciousness and lack of recall, and by the opioid providing an adequate concentration to obtund reflex response to the noxious stimulus. This supports the concept of the triad of anesthesia: unconsciousness and lack of recall, analgesia, and muscle relaxation.[11] It is now well recognized that individual anesthetics each produce a unique spectrum of pharmacologic actions, so the concept of a common "depth of anesthesia" may need to be revised to reflect the separate clinical components of the ideal anesthetic state. Consequently, a monitor of depth of anesthesia may only measure one of these components, such as loss of consciousness, obtunding of noxious reflexes, or neuromuscular blockade.

The bispectral index (BIS) is a derived variable of the EEG that has been reported possibly to be related to the hypnotic component of the anesthetic state.[12,13] This study was designed to clearly define the relation among clinical assessment of the state of consciousness, explicit recall, drug concentrations, and EEG effects of four commonly used anesthetic drugs when administered alone to healthy volunteers under controlled experimental conditions.

Methods

This was a prospective study conducted in healthy volunteers at four separate sites. Institutional review board approval was obtained at each site, and all volunteers gave written informed consent. The evaluable patient population consisted of 70 (minimum of ten persons per anesthetic agent) paid healthy male or female volunteers. Those with known neurological disorders, including current use of anticonvulsant or other psychoactive medications; long-term drug or alcohol use; clinically significant hypertension; or other serious medical conditions that would interfere with response analysis were excluded.

All volunteers underwent a history and physical examination before being enrolled in the study. All were instructed to remain *nil per os* from midnight the night before the study. On the morning of the study, volunteers had an intravenous catheter inserted for fluid and drug administration. A radial arterial catheter was also inserted into each one, except those given isoflurane, to monitor blood pressure and to obtain blood samples for subsequent measurement of drug concentration. In the volunteers administered isoflurane, blood pressure was monitored using an automated blood pressure cuff. The volunteers were also monitored using a standard three-lead electrocardiograph, a peripheral pulse oximeter for $Sp0_2$, and nasal prongs or a tight-fitting face mask for end-tidal carbon dioxide and to supply supplemental oxygen. An observer monitored respiratory and cardiovascular function and determined the need for interventions such as jaw support to maintain an adequate airway.

An EEG signal was acquired using gold cup electrodes applied to the scalp with collodion or cream, with skin impedance maintained at less than 5 KOhms. The following leads were recorded: Fp1, Fp2, with CZ as the reference (channels 1 and 2) and two additional frontal locations between the preauricular point and the outer corner of each eye using "Fpz" as the reference (channels 3 and 4) plus a ground electrode. The EEG was recorded continuously using an Aspect A-1000 EEG monitor (Aspect Medical Systems, Natick, MA). Data averaged from the combined bifrontal leads (channels 1 and 2) are presented in this article, although similar results were obtained from all channels.

Serial output files consisting of digitized raw EEG and real-time, processed EEG parameters were collected on a personal computer, as were time-synchronized markers describing all clinical assessment events. Drug infusion data were also collected in a similar manner, thereby allowing for a full description of each volunteer's drug delivery history, EEG, and clinical response profile on a minute-by-minute basis.

Data were analyzed using two versions of the BIS. The BIS (revision 2), which has been described previously,[12] was calculated in real time using standard A-1000 monitor software. Samples of raw EEG recordings from this study were also used to develop an updated BIS algorithm. This algorithm was then used to reprocess the raw EEG recordings to produce a new BIS 3.0 profile for every case (see Appendix 1). The BIS levels recorded immediately (10–30 s) before the start of each clinical assessment were used for subsequent statistical data analysis.

Once all monitoring had been instituted, the volunteers were given a 15-minute resting period. Thereafter baseline readings were obtained. These consisted of a sedation score using the responsiveness component of the Observer Assessment of Alertness and Sedation rating scale (table 1). This assessment procedure involves presentation of progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimuli (trapezius squeeze), until a response is observed. Other baseline readings included loss of eyelash reflex, arterial blood sample (2 two samples per drug level), and a picture/word recall test.

Participants were asked to remember a unique, randomly chosen picture or word at each assessment. After recovery at the end of the study, the participants were asked to remember all pictures or words they were given during the study (correct responses were considered evidence of free recall). They were then shown a list containing the target items as well as similar "distracters" that were not used during the study. Volunteers were asked only to list an item if they could recall it and not to pick any item. Correct identification (recognition) of items actually presented during the study was considered evidence of cued recall. Patients having no free or cued recall were classified as having complete lack of recall (no memory) in subsequent analysis.

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/sedation Scale

Response	Score Level
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

The effect of isoflurane, propofol, midazolam, and alfentanil on the BIS score and level of sedation was evaluated. The intravenous drugs (propofol, midazolam, and alfentanil) were administered *via* a target-controlled infusion device (either CACI[14] or STANPUMP[15]) to a target effect site concentration. Isoflurane was administered *via* a tight-fitting mask using a calibrated vaporizer through a semiclosed non-rebreathing circuit. End-tidal isoflurane concentration was monitored using a Rascal 2 agent analyzer (Albion Instruments, Salt Lake City, Utah). Isoflurane was administered in steps to achieve loss of consciousness (*i.e.*, OAAS score of 2 or less) by increasing the end-tidal concentrations to 0.25%, 0.5%, 0.75%, and 1%. Once loss of consciousness had been achieved, the end-tidal isoflurane concentration was decreased by the same steps until consciousness was regained. The isoflurane concentration was again increased until loss of consciousness occurred again and then decreased so that at least two crossovers in consciousness occurred for each volunteer.

Propofol was similarly administered in increasing steps to target effect site concentrations of 1, 2, 4, and 6 μg/ml until volunteers lost consciousness. The

Table 2. Demographic Summary of Subjects Enrolled in each Volunteer Study Protocol

Site	Duke University Medical Center	Duke University Medical Center	Duke University Medical Center	Massachusetts General Hospital	Emory University	University of Pittsburgh
Drug regimen	Midazolam	Alfentanil	Propofol	Propofol	Propofol	Isoflurane
Number	10	10	10	20	10	10
Male	7	8	5	15	4	7
Female	3	2	5	5	6	3
Mean age, ± SD	29 ± 8	25 ± 6	31 ± 6	33 ± 9	30 ± 4	31 ± 9
Age range	20–41	19–38	23–41	22–50	23–39	22–45
Mean weight ± SD, kg	74 ± 10	75 ± 14	72 ± 20	74 ± 13	71 ± 14	80 ± 14
Weight range, kg	56–88	58–102	46–115	51–109	44–92	61–100

SD = standard deviation.

propofol concentration was decreased by the same steps until consciousness occurred and then increased and decreased so that at least two crossovers of consciousness/unconsciousness occurred. Midazolam and alfentanil were administered *via* a slightly different protocol. Midazolam was administered in a stepwise manner to target effect site concentrations of 0, 75, 150, 300, and back down to 150 ng/ml. Alfentanil was administered in a similar stepwise manner to target effect site concentrations of 0, 50, 100, 200, and back down to 100 ng/ml. At each step, the target concentration was maintained for a minimum of 10 min to ensure equilibration with the effect site. Drug plasma concentrations were determined from the arterial blood samples collected at the end of each steady-state assessment period. The following analytical methods were used:

Propofol

Propofol determinations were made using high-powered liquid chromatography analysis at the Anesthesia Research Laboratory at Duke University Medical Center. The separation and quantification procedures was conducted with a C-18, 15 cm × 4.6 mm column (Supelcosil LC-18; Supelco, Bellefonte, PA) and detection was fluorometric. Spiked standards (0.5 and 5 g/ml) were required to be within 20% of the true value with an interassay variability of 12%. The duplicate assays of the participant samples were required to be within 20% of each other.

Midazolam

Midazolam and alfentanil assays were performed at North Carolina State University. Midazolam samples were assayed by gas chromatography with an electron capture detector according to the method of Greenblatt *et al.*[16] Interassay variability was less than 10.1%.

Alfentanil

Plasma samples were measured in duplicate by radioimmunoassay using kits from Janssen Pharmaceutical (Olen, Belgium). Interassay variability averaged 11.2% over the therapeutic range of concentrations.

Results were analyzed for each drug to determine agent-specific relations among the EEG, measured drug concentration, and the hypnotic and memory end points. Readings for BIS obtained during the second blood sample (when arousal had occurred due to stimulation of the volunteer) or outside of the protocol when a steady state had not yet been achieved were excluded from any data analysis because they may have negatively biased the relation between responsiveness score and drug concentration. Linear correlations between variables at each assessment point were first examined. All volunteers who responded to any verbal command (sedation categories 3, 4, and 5) were classified as conscious. Those who did not respond (sedation scores of 0, 1, and 2) were considered to be unresponsive and unconscious. Logistic regression techniques were used to analyze these relations for quantal end points such as loss of consciousness and lack of recall. The means and 95% confidence intervals (CIs) surrounding the BIS_{50} and BIS_{95} values were calculated using the covariance matrix of the logistic regression parameters to estimate the standard error of the predicted estimates of BIS_{50} and BIS_{95} (SAS Stat User's Guide; SAS Institute, Cary, NC). The prediction probability was also determined as described by Smith *et*

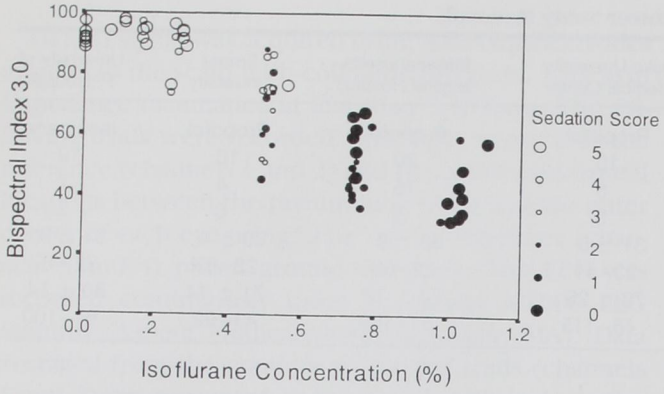

Fig. 1. Scatter diagram showing the relation among BIS, expired isoflurane concentration (%), and sedation scores. Each point represents one assessment. Open circles represent observations classified as conscious (responds to verbal command), whereas filled circles are considered unconscious.

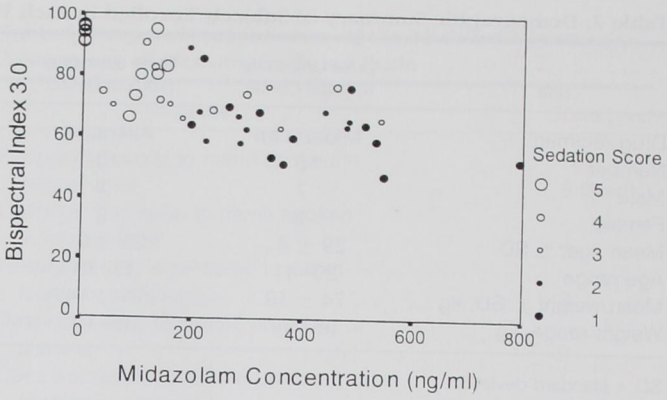

Fig. 3. Scatter diagram showing the relation among BIS, measured midazolam concentration (ng/ml), and sedation scores. Each point represents one assessment. Open circles represent observations classified as conscious (responds to verbal command), whereas filled circles are considered unconscious.

al.[17] Any systematic differences among the groups and drugs were analyzed using analysis of variance or *t* tests when appropriate. Because no significant differences were observed for the relation between BIS and consciousness or unconsciousness for propofol, isoflurane, and midazolam, data from these three treatment groups were pooled to derive the common relation between responsiveness score and BIS. Descriptive statistics were used to characterize demographic variables of each of the study groups. Probability values less than 0.05 were considered significant.

Results

Seventy-two volunteers were enrolled at the four sites of this study. Table 2 shows the demographic distribution of participants at each study site. Two volunteers were withdrawn from the study prematurely (and subsequently replaced) when signs of an irritable airway (isoflurane group) and early airway obstruction (propofol group) were noted at low dose levels. Further dose increases were not attempted in these persons and they recovered fully without adverse sequelae.

Figures 1 to 4 show the relation among BIS 3.0, mea-

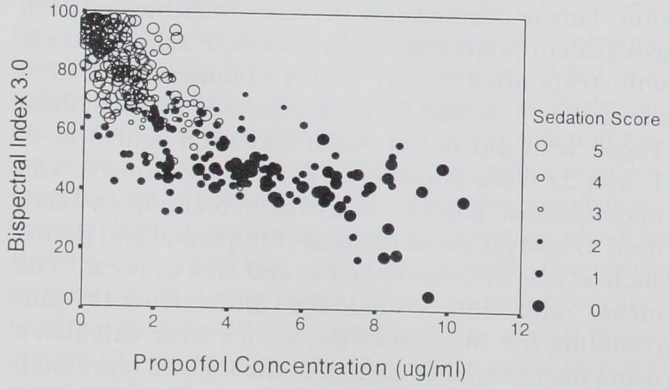

Fig. 2. Scatter diagram showing the relation among BIS, measured propofol concentration (μg/ml), and sedation scores. Each point represents one assessment. Open circles represent observations classified as conscious (responds to verbal command), whereas filled circles are considered unconscious.

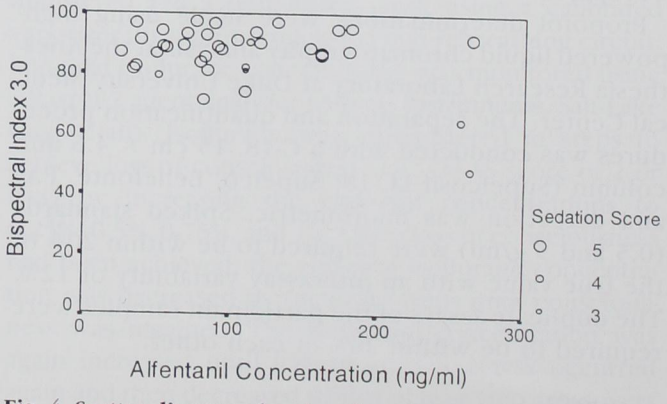

Fig. 4. Scatter diagram showing the relation among BIS, measured alfentanil concentration (ng/ml), and sedation scores. Each point represents one assessment. Open circles represent observations classified as conscious (responds to verbal command). All participants remained conscious during the study.

Table 3. Comparison of the Linear Correlations Coefficients Between Measured Drug Concentration, or BIS, and the Clinical Sedation Scores as Shown in Fig. 1–4; Correlation (r) with Responsiveness Score

Agent (n)	BIS 3.0	BIS 2.5	Target Concentration	Measured Concentration	Log Concentration
Propofol (399)	0.883*†‡	0.912*†‡	−0.808	−0.778	−0.769
Isoflurane (70)	0.850	0.828*†‡	−0.890	−0.894	−0.846
Midazolam (50)	0.755	0.700	−0.773	−0.746	−0.654
Alfentanil (50)	0.444*‡	0.434*‡	−0.166	−0.254	−0.235

* Significantly different than the correlation of Target Concentration with Sedation Score ($P \leq 0.05$).

† Significantly different than the correlation of Measured Concentration with Sedation Score ($P \leq 0.05$).

‡ Significantly different than the correlation of Log Measured Concentration with Sedation Score ($P \leq 0.05$).

sured drug concentration, and sedation score at each assessment point. Table 3 also summarizes this information. Figures 5 and 6 show logistic regression curves describing the probability of loss of consciousness and recall *versus* BIS 3.0 for each agent. The logistic regression curves for absence of lash reflex were indistinguishable from the probability of loss of consciousness curves. The prediction probability values for BIS, which indicate the probability of correctly predicting the state of consciousness *versus* loss of consciousness with the drugs tested, ranged from 0.885-0.976 and are listed in table 4.

Table 5 lists the BIS 3.0 values for each drug at which 50% and 95% of volunteers were unconscious (BIS_{50} and BIS_{95}, respectively) and demonstrated complete lack of recall. No values could be derived for participants receiving alfentanil, because only two of them across all dose levels had loss of cued recall and no participant lost consciousness. Because no significant differences among agents were observed, the propofol, isoflurane, and midazolam groups were combined to yield a BIS_{50} for loss of consciousness of 65 (95% CI, 64.6-65.4) and a BIS_{95} of 51 (95% CI, 46.9-51.5). The BIS_{50} and BIS_{95} values for complete lack of recall (*i.e.*, the BIS value at which there is a 50% or 95% probability of no free or cued recall) when all drugs were combined were 86 (95% CI, 85.0-87.4) and 64 (95% CI, 51.8-68.6), respectively. Figure 7 shows the logistic regression curves

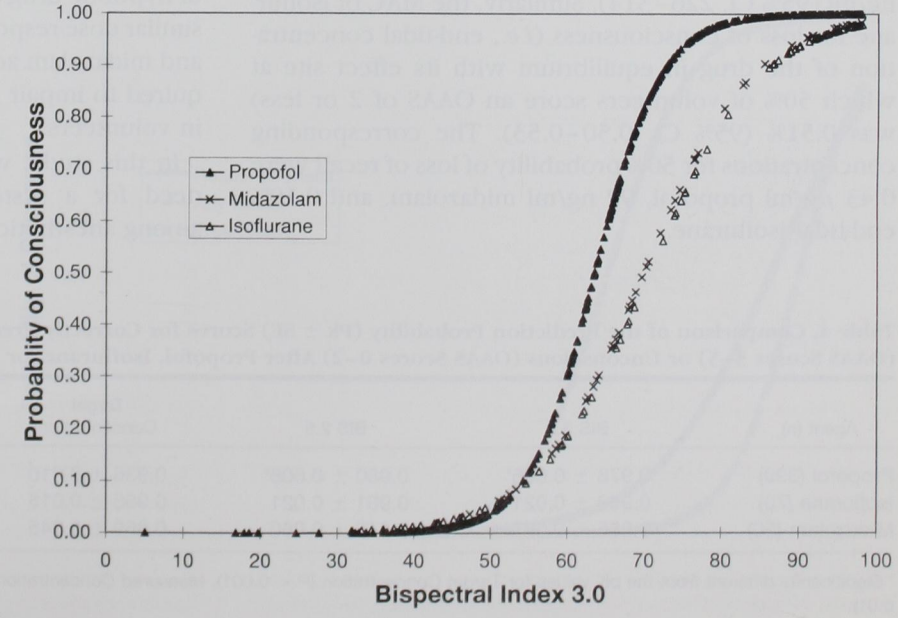

Fig. 5. Relation between BIS and probability of a positive response (0 to 1.0 = 0–100% probability) to verbal command determined using logistic regression analysis of a quantal end point (conscious/unconscious) for all volunteers receiving propofol, isoflurane, or midazolam. All volunteers receiving alfentanil remained conscious during the study, so no logistic curve could be derived.

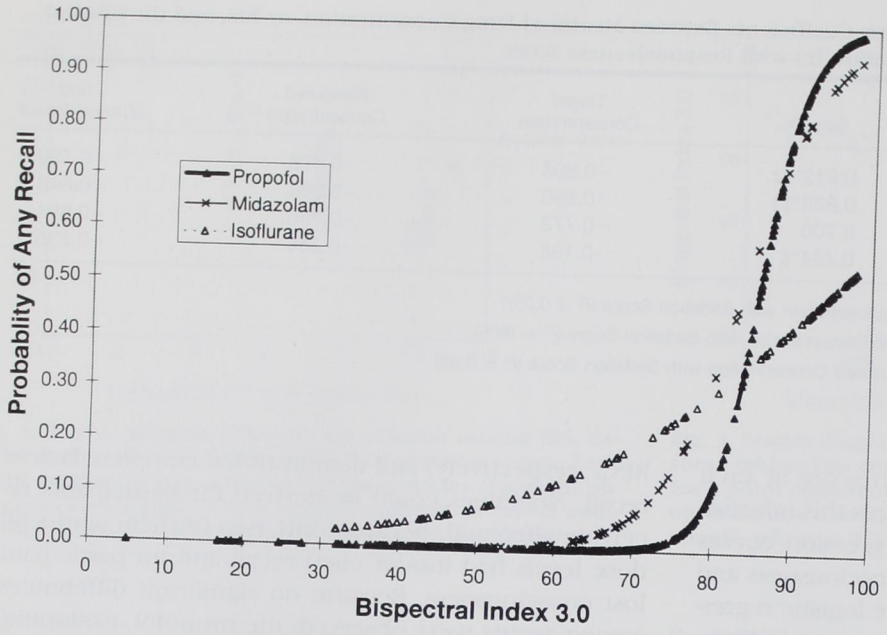

Fig. 6. Relation between BIS and probability of a positive response (0 to 1.0 = 0–100% probability) determined using logistic regression analysis of a quantal end point (free or cued recall/no recall) for all volunteers receiving propofol, isoflurane, or midazolam. For participants receiving alfentanil, recall was present for 38 of 40 assessments, so no logistic relation could be derived. The relatively flat appearance of the isoflurane curve is due to one positive cued recall outlier event with a BIS score of 35 (see Discussion).

describing the probability of loss of consciousness and recall *versus* BIS when the data for propofol, isoflurane, and midazolam are combined.

The Cp_{50} for loss of loss of consciousness/unconscious (i.e. plasma concentration of the drug in equilibrium with its effect site at which 50% of participants score an OAAS of 2 or less) for propofol was 2.35 μg/ml (95% CI, 2.28–2.43) and for midazolam it was 270 ng/ml (95% CI, 226–314). Similarly, the MAC of isoflurane for loss of consciousness (*i.e.*, end-tidal concentration of the drug in equilibrium with its effect site at which 50% of volunteers score an OAAS of 2 or less) was 0.51% (95% CI, 0.50–0.53). The corresponding concentrations for 50% probability of loss of recall were 0.43 μg/ml propofol, 92 ng/ml midazolam, and 0.19% end-tidal isoflurane.

Discussion

Results from this volunteer trial provide a quantitative comparison of the correlations among drug concentrations, BIS, and clinical measures of sedation and memory function for four widely used anesthetic agents. These results show that the BIS, a value derived from the EEG, can be used as a pharmacodynamic measure of hypnotic drug effect. Most importantly, BIS showed a similar dose-response relation with isoflurane, propofol, and midazolam across the dose/concentration range required to impair memory and induce unconsciousness in volunteers.

In this study, we address the previously recognized need for a systematic investigation of the relation among anesthetic drug concentration, EEG parameters,

Table 4. Comparison of the Prediction Probability (Pk ± SE) Scores for Correctly Predicting Whether Subjects Were Conscious (OAAS Scores 3–5) or Unconscious (OAAS Scores 0–2) After Propofol, Isoflurane, or Midazolam Administration.

Agent (n)	BIS 3.0	BIS 2.5	Target Concentration	Measured Concentration	Log Concentration
Propofol (399)	0.976 ± 0.006*	0.980 ± 0.006*	0.936 ± 0.010	0.937 ± 0.013	0.933 ± 0.014
Isoflurane (70)	0.959 ± 0.021	0.961 ± 0.021	0.965 ± 0.015	0.967 ± 0.016	0.956 ± 0.021
Midazolam (50)	0.885 ± 0.047	0.846 ± 0.060	0.869 ± 0.045	0.886 ± 0.048	0.832 ± 0.068

* Significantly different from the pK values for Target Concentration ($P < 0.001$), Measured Concentration ($P < 0.01$), and Log Measured Concentration ($P < 0.01$).

Table 5. Mean and 95% Confidence Intervals Surrounding the BIS_{50} and BIS_{95} Values, Calculated Using the Covariance Matrix of the Logistic Regression Parameters to Estimate the Standard Error of the Predicted Estimates of BIS_{50} and BIS_{95}; BIS_{50} and BIS_{95} Values for Loss of Consciousness and Recall

		BIS_{95} (95% CI)	BIS_{50} (95% CI)
BIS 3.0			
Consciousness	Propofol	51 (48–55)	63 (62–65)
	Isoflurane	50 (39–61)	71 (65–76)
	Midazolam	49 (37–62)	70 (65–75)
	Combined	50 (46–53)	65 (63–67)
Recall	Propofol	77 (72–83)	86 (83–88)
	Isoflurane	42 (13–71)	95 (81–100)
	Midazolam	68 (59–78)	84 (78–89)
	Combined	64 (57–71)	86 (83–89)
BIS 2.5			
Consciousness	Propofol	55 (51–58)	70 (67–72)
	Isoflurane	56 (46–67)	74 (69–80)
	Midazolam	56 (43–69)	76 (71–81)
	Combined	55 (51–59)	71 (69–73)
Recall	Propofol	76 (67–84)	89 (86–91)
	Isoflurane	48 (22–74)	94 (82–100)
	Midazolam	73 (63–82)	86 (82–91)
	Combined	64 (55–73)	89 (86–92)

and clinical measures of depth of anesthesia for individual anesthetic drugs.[4] Previous reports have shown that BIS is a useful predictor of patient response (movement or increased blood pressure) during surgery using various anesthetic regimens.[18–22] However, in a large, prospective multicenter study using movement response as a clinical end point, it was noted that BIS seemed to correlate best with the effects of hypnotic drugs (isoflurane, propofol), whereas opioid analgesics attenuated movement at dose levels that had little effect on the EEG.[23] This suggested that movement at incision primarily reflects the ability of the drug to obtund noxious reflexes and may not be the most appropriate measure for assessing the consciousness/loss of consciousness effects of many anesthetics. This study contrasts with most previous studies evaluating the utility of BIS (or other EEG parameters) in that we evaluated the relation among increasing levels of sedation (as determined by the responsiveness measure of the OAAS), drug concentration, and BIS.

The OAAS scale was chosen because it provides a good correlation with the clinical evaluation of sedation and has been tested prospectively.[24] In our initial analysis, it was assumed that this scale would provide a linear correlation between the observed clinical effect and the BIS value or drug concentration. Recently the techniques used to evaluate performance of anesthetic depth indicators was reviewed.[17] As discussed by Smith *et al.*,[17] ordinal values obtained using a responsiveness rating scale may not allow a perfect linear relation be-

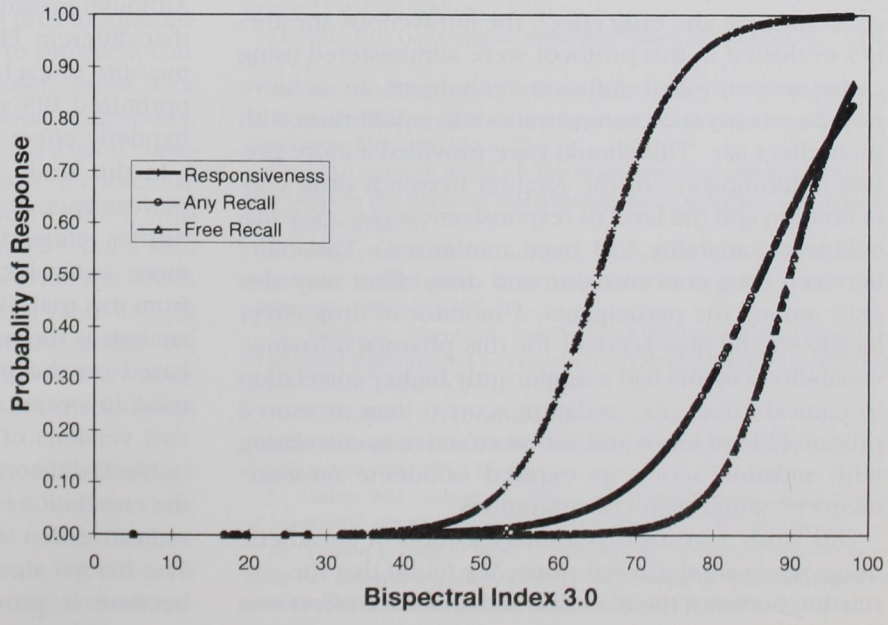

Fig. 7. Relation between BIS and probability of a positive response (0 to 1.0 = 0–100% probability) determined using logistic regression analysis of quantal end points (loss of consciousness or recall) for the pooled analysis of data from all volunteers receiving propofol, isoflurane, or midazolam.

tween the observed effect and the measure of anesthetic depth. To account for this uncertainty, they proposed calculating a prediction probability value, which may provide a better measure to monitor performance. The prediction probability value for BIS with the drugs for which loss of response occurred ranged from 0.885 (for midazolam) to 0.976 (for propofol). The good correlation between BIS and level of sedation, coupled with the excellent prediction probability values, supports the value of the BIS to monitor increasing sedation and loss of consciousness.

In a preliminary report from this trial,[25] we noted that increasing intensity of stimulation applied during this clinical assessment process can lead to participant arousal, thereby resulting in a variable clinical state despite maintenance of constant drug levels. These factors undoubtedly contributed to the observed intersubject variability for all the quantitative measures, especially near the critical transition between consciousness and unconsciousness. In addition, the assessment of sedation was done by several observers at four institutions in an open study. This type of study design could also lead to observer bias and variability in assessing sedation levels. Despite these potential sources of inherent variability in the assessment and description of clinical state, consistent relations between the BIS and other measures of drug effect were observed for each of the drugs.

To reduce intersubject variability resulting from drug dose and the hysteresis that may exist between plasma concentration and drug effect, the intravenous anesthetics evaluated in this protocol were administered using computer-controlled infusion techniques to achieve pseudo-steady-state concentrations in equilibrium with their effect site. This should have provided a more precise determination of the relation between drug concentration and the level of responsiveness (*i.e.*, pharmacokinetic variability had been minimized). Variability between drug concentration and drug effect may also exist among the participants. A monitor of drug effect ideally should also account for this pharmacodynamic variability. The BIS had a significantly higher correlation to clinical effect (*i.e.*, sedation scores) than measured propofol blood levels and was as effective in correlating with sedation scores as expired isoflurane measurements or midazolam concentrations.

This study investigated a cross section of anesthetic drugs when administered alone. We found that the correlation between the BIS value and measured effect was independent of the drug administered to induce sedation. Similar probability of response curves were obtained for propofol, midazolam, and isoflurane. When these anesthetics are used alone, BIS values greater than 70 are associated with a high probability of response to verbal stimulus, whereas values less than 50 indicate a low probability of response to verbal command. Across all drugs tested, BIS values less than 64 were associated with a low probability of recall. In a study evaluating midazolam alone in the presence of regional anesthetic block, the BIS_{50} for loss of consciousness was 79.3.[13] This value is somewhat higher than that obtained for our group of midazolam alone (BIS_{50} = 70) and the combined agent BIS_{50} of 65. This difference may reflect either the influence of the regional block in attenuating sensory input or the louder verbal commands that can be used in a volunteer study setting compared with those used during surgery. Leslie *et al.*[26] reported a BIS_{50} of 91 for propofol-induced suppression of learning using a "Trivial Pursuit" type of question task that is similar to the BIS_{50} of 86 that we obtained using a picture or word recall test.

Our observation that the BIS *versus* clinical response relation is independent of the choice of anesthetic drug is encouraging for its clinical utility. However, modern anesthesia is provided by a combination of several drugs, and it will be equally important to determine if the relation between the BIS and sedation remains independent of drug when drug combinations are used. Although previous work from several groups suggested that different EEG descriptors might provide the best measure of each drug effect, we sought to evaluate an optimized BIS variable as a common measure of the hypnotic effect induced by all three drug classes.

In this study, we prospectively tested the real-time performance of one BIS version (revision 2.5) and then further refined the BIS algorithm (revision 3.0) using a more extensive database that included observations from this trial. One potential drawback of retrospective analysis is the possibility of introducing significant bias based on the particular composition of the database used to optimize performance. Comparison of these two versions of BIS in this population of participants (table 3) did not result in any significant improvement in the correlation between BIS and patient responsiveness, indicating that significant bias had not been introduced. The BIS 3.0 algorithm has been selected for future use because it provided a better performance at more

awake levels of the responsiveness score, as described in the appendix.

The drug concentration ranges required to interfere with memory function and induce unconsciousness in this study are consistent with previous published reports concerning each of the drugs.[27-32] Our results confirm that midazolam, propofol, and isoflurane produce amnestic effects at concentrations that are insufficient to induce loss of consciousness. We recognize that relatively simple tests of memory function (picture or word recall) were used in this study, so it is possible that some "implicit" memory function may have been preserved even when volunteers appeared to be unconscious. For example, one volunteer correctly recognized (cued recall test) the word *snake*, which had been presented after he had been at a steady-state end-tidal isoflurane concentration of 1% for at least 11 min. During this assessment period, he had a sedation score of 0 (no response to trapezius squeeze) and a BIS of 35. We assume that he simply guessed correctly when shown the list of presented words, because he had no specific recollection of having heard the word *snake*, but we cannot eliminate the possibility that some form of implicit priming may have occurred.

Ideally a monitor of anesthetic depth should (1) have a perfect correlation between the measured effect and the value obtained by the monitor, (2) this correlation should be independent of the drug administered, and (3) there should be no interpatient variability. Does BIS achieve this ideal monitor? Adequate anesthesia appears to depend on providing an adequate concentration of a drug to suppress reflex responses to noxious stimuli and to provide a concentration of drug to ensure loss of consciousness. Our results show that during the administration of propofol, isoflurane, and midazolam, the BIS provided a good correlation with the level of responsiveness, loss of consciousness and recall that was drug independent, albeit with some degree of intersubject variability. Initial reports with drug combinations commonly used to provide anesthesia have reported a small increase in the BIS_{50} value for loss of consciousness.[33,34] The results from these studies are sufficiently encouraging to suggest that BIS is likely to be helpful in guiding titration of the loss-of-consciousness component of the anesthetic.

In summary, this study showed that the BIS correlated well with the effects of propofol, midazolam, and isoflurane on level of consciousness and recall. The correlation of BIS to the level of sedation is equal to, or better than, using measured drug concentrations. Across all drug combinations, BIS levels less than 50 indicate that a participant is probably unconscious and will have no recall. Therefore we believe that the BIS may be used effectively to measure the absence of consciousness after midazolam, propofol, or isoflurane.

References

1. Snow J: On the inhalation of vapors of ether in surgical operations. Containing a description of the various stages of etherization and a statement of the results of nearly eighty operations in which ether has been employed at St. George's and University College hospitals. London, John Churchill, 1847, 1-15

2. Snow J: On chloroform and other anesthetics. London, John Churchill, 1858, i-xliv

3. Guedel AE: Inhalational anesthesia, A fundamental guide. New York, Macmillan, 1937

4. Stanski DR: Monitoring depth of anesthesia, Anesthesia, Third edition. Edited by Miller RD. New York, Churchill Livingston, 1990, pp 1127-59

5. Prys-Roberts C: Anesthesia: A practical or impractical construct? Br J Anaesth 1987; 59:1341-5

6. Kissin I: General anesthetic action: An obsolete notion? Anesth Analg 1993; 76:215-18

7. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. ANESTHESIOLOGY 1993; 78:707-12

8. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. ANESTHESIOLOGY 1993; 79:1244-9

9. McEwan AI, Smith C, Dyar O, Goodman D, Glass PSA: Isoflurane MAC reduction by fentanyl. ANESTHESIOLOGY 1993: 78;864-9

10. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PSA: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. ANESTHESIOLOGY 1994; 81:820-8

11. Hug CC: Does opioid anesthesia exist? ANESTHESIOLOGY 1990; 73:1-4

12. Greenwald S, Chiang HH, Devlin P, Smith C, Sigl J, Chamoun N: Bispectral index (BIS2.0) as a hypnosis measure (Abstract). ANESTHESIOLOGY 1994; 81(3A):A477

13. Lui J, Singh H, White PF: Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. ANESTHESIOLOGY 1996; 84:64-9

14. Glass PSA, Jacobs JR, Reves JG: Intravenous anesthetic delivery, Anesthesia Third Edition. Edited by Miller R. New York, Churchill Livingston, 1990, pp 367-88

15. Shafer SL, Varvel JR, Aziz N, Scott JC: The pharmacokinetics of fentanyl administered by computer controlled infusion pump. ANESTHESIOLOGY 1990; 73:1091-1102

16. Greenblatt DJ, Locniskar A, Ochs HR, Lauven PM: Automatic gas chromatography for studies of midazolam pharmacokinetics. ANESTHESIOLOGY 1981; 55:176-9

17. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38-51

18. Vernon J, Lang E, Sebel P, Manberg PJ: Prediction of movement using BIS electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 1995; 80:780-5

19. Kearse LA, 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

20. Sebel PS, Bowles SM, Saini V, Chamoun N: EEG Bispectrum predicts movement during thiopental/isoflurane anesthesia. J Clin Monit 1995; 11:83–91

21. Vernon JM, Lang E, Sebel PS, Manberg PJ: Prediction of movement using bispectral EEG analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 1995; 80:780–5

22. Kearse LA, 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. Electroenceph Clin Neurophysiol 1994; 90:194–200

23. Sebel PS, Rampil I, Cork R, White PF, Smith NT, Glass P, Jopling M, Chamoun N: Bispectral analysis (BIS) for monitoring anesthesia: Comparison of anesthetic techniques (Abstract). ANESTHESIOLOGY 1994; 81:A1488

24. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the observer's assessment of alertness/sedation scale: Study with intravenous midazolam. J Clin Psychopharmacol 1994; 10:244–51

25. Bloom MJ, Kearse L, Rosow C, Sebel P, Glass P, Devlin P, Greenwald S: Bispectral index measures EEG changes due to response to stimulus (Abstract). ANESTHESIOLOGY 1995; 83:A516

26. Leslie K, Sessler DI, Schroeder M, Walters K: Propofol blood concentration and the bispectral index predict suppression of learning during propofol/epidural anesthesia in volunteers. Anesth Analg 1995; 81:1269–74

27. Vessen A, Persson PM, Nilsson A, Hartvig P: Concentration-effect relationships of propofol after total intravenous anesthesia. Anesth Analg 1993; 77:1000–7

28. Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF: EEG and memory effects of low dose infusions of propofol. Br J Anaesth 1992; 69:246–54

29. Persson MP, Nilsson A, Hartvig P: Relation of sedation and amnesia to plasma concentrations of midazolam in surgical patients. Clin Pharmacol Ther 1988; 43:324–31

30. Dwyer R, Bennett HL, Eger EI, Peterson N: Isoflurane anesthesia prevents unconscious learning. Anesth Analg 1992; 75:107–12

31. Chortkoff BS, Eger E, Crankshaw DP, Gonsowski T, Dutton RC, Ionescu P: Concentrations of desflurane and propofol that suppress response to command in humans. Anesth Analg 1995; 81:737–43

32. Kearse L, Rosow C, Glass P, Sigl J: Monitoring changes in EEG bispectral index correlate with targeted plasma concentrations of propofol and midazolam (Abstract). Anesth Analg 1996; 82:S220

33. Kearse LA Jr, Rosow C, Connors P, Denman W, Dershwitz M: Propofol sedation/hypnosis and bispectral EEG analysis in volunteers. (Abstract). ANESTHESIOLOGY 1995; 83:A506

34. Howell S, Gan TJ, Martell D, Glass P: Defining the Cp50 and BIS50 for propofol alone and propofol plus alfentanil (Abstract). ANESTHESIOLOGY 1995; 83:A367

Appendix 1. Bispectral Index (Revision 3.0) Development

Clinical Database

A large database of high-fidelity EEG recordings was collected from patients or volunteers receiving a wide variety of anesthetic regimens. From this large database ($n > 600$), a heterogeneous subset of cases ($n = 215$), including 70 cases from this volunteer study, were selected for inclusion in a development database. Selection of cases was based on the following criteria: availability of complete clinical records, use of a frontal montage, distribution of representative anesthetics, and assessment of sedation/hypnotic end points. Anesthetic regimens included in this development database included propofol, isoflurane, midazolam, and thiopental, supplemented with various amounts of opioids and nitrous oxide. The database consisted of 1,223 EEG segments of 100 s each recorded at multiple electrode sites from 215 patients, totaling more than 33 h of EEG recordings. The database therefore consists of a segment of EEG and an associated, clinically derived hypnotic/sedation state.

Learn/Test Paradigm

The development database was divided in thirds to form three data sets: two retrospective development sets (*i.e.*, a learning set A and a testing set B), and a prospective evaluation set (C). Two retrospective sets were created to allow a pseudo-prospective evaluation on set B of indices developed using set A (*i.e.*, a learn/test paradigm). Set C was reserved for the final prospective statistical evaluation of candidate indices that occurred at the end of the development process. An equal number of patients were randomly assigned to each data set, controlling for anesthetic protocol.

Feature Extraction

The segments of EEG immediately preceding each of the 1,223 observation points (*i.e.*, snippet) were used to compute candidate parameters, or features, for evaluation. A set of candidate bispectral and power spectral features were extracted from the last 60 artifact-free seconds of each 100-s EEG snippet. The power spectrum and bispectrum of the EEG snippet data were computed and divided into regions of different sizes of frequency (*e.g.*, the value of the power spectrum between 10 and 20 Hz). A series of different parameters (mean, maximum, and so on) were used to characterize the data in the frequency bands.

Feature Selection

The ability of each member of the set of candidate features to discriminate between sedation groups was assessed by a multivariate step-wise regression (using SPSS Release 6.0, SPSS Inc., Chicago, Illinois, running on a Sun Microsystems Sparc System, Burlington, Massachusetts) with sedation level using development set A. The observation points were equally weighted by sedation group. The features were ranked by the multiple regression coefficient (multiple R). In addition to individual features, the scope of the multivariate regression was expanded to incorporate interaction terms of two features. The interaction terms often resulted in higher multiple Rs than did their components considered individually.

Combination of Features into an Index

The features and interaction terms that produced high correlations with sedation level ($R > 0.80$) on set A were combined into multivariate indices using a multivariate regression to estimate the regression coefficients. The algorithm of the loss of consciousness/sedation index is:

$$\text{Index} = a1*\text{feature1} + a2*\text{feature2} + a3*\text{feature3} + c$$

where a1, a2, and a3 are the coefficients of the first, second, and third features and c is a constant. Feature 1 is a low-frequency bispectral feature associated with "deep" anesthetic effect. This feature is a normalized measure of the relative consistency of the relations among the very low (<1 Hz) and the very high (40–47 Hz) frequency components. Feature 2 is a high-frequency feature associated with light anesthetic effect and beta activation. It is an aggregate measure of the activity of the components in the middle frequencies (11–20 Hz) relative to the activity of the components in the very high frequencies (40–47 Hz). Feature 3 is the degree of EEG suppression. The proprietary coefficients and the constant are determined by the multivariate regression model.

The candidate index developed using set A was evaluated by determining its classification performance on set B. This helped to ensure that the set of EEG features selected for a candidate index were statistically significant for the anesthetic regimens represented in the clinical database. Full case trends on a subset of cases were generated for candidate indices that exhibited good classification performance on both retrospective development sets. Candidate indices with poor trending performance were rejected.

The loss of consciousness/sedation model was developed using only segments of artifact-free, nonsuppressed EEG. To evaluate the performance of the revised BIS on nonideal data, final validation of the combined index was performed by trending the index on prospective databases containing all types of EEG. Trending was performed on cases included in the trending databases (n = 429). Therefore, even though about 33 h of EEG data were used for the development database, evaluation of performance was conducted on more than 1,000 h of EEG recordings.

The best candidate index based on statistical and trending performance was selected as the revised BIS and is called BIS 3.0. In contrast to earlier versions of the BIS, the addition of the high-frequency feature yields an index that decreases monotonically with increasing dose of hypnotic agent, even in the light sedation levels in which beta activation may occur. The result is a BIS with an improved correlation with light sedation/anesthetic levels. Although these index refinements have improved performance in the lighter sedation ranges, intraoperative trending performance remains similar to previous versions.