Can We Monitor Depth of Anesthesia?

Peter S. Sebel, MB, BS, PhD, MBA

Introduction

Measurement of depth of anesthesia is a somewhat difficult concept. We are hindered by the fact that we are not entirely sure what we are measuring. Compare, for example, the measurement of blood pressure. Pressure is measured in known units (millimeters of mercury), and we have various standards and can compare the performance of different blood pressure measuring devices. In contrast, there are no obvious apparent units for the measurement of depth of anesthesia. Indeed, we may argue about the exact components of the anesthetic state. The purpose of this review is to discuss the components of the anesthetic state, to determine which aspects of the anesthetic state are amenable to measurement, and to review the performance of technologies available for such measurement.

The Anesthetic State

We generally understand the anesthetic state to consist of a reversible state of unconsciousness, during which a patient will not perceive or be responsive to noxious stimuli. Although we often (to patients) interchangeably use the terms "going to sleep" and "induce anesthesia," they are not the same. If you are asleep and somebody assaults you with a knife, then you wake up. If you are adequately anesthetized, then you should be unresponsive to such a noxious stimulus. Gray and Rees, in 1952 (1), considering the concept of balanced anesthesia, proposed the triad of amnesia, analgesia, and reflex suppression. Muscle relaxation is often considered to be a part of the anesthetic state, but it is not necessarily so.

As far as signs of inadequate anesthesia are concerned, a movement response to surgical stimulation has generally been held to be an unequivocal sign of inadequate anesthesia. However, there is good evidence that movement response is mediated at the spinal cord level. Rampil (2) demonstrated that, after spinal cord transection, the concentration of isoflurane required to suppress movement in 50% of rats (minimum alveolar anesthetic concentration) was not altered. Similarly, minimum alveolar anesthetic concentration of isoflurane is not altered after removal of the forebrain (3). We also know that relatively large doses of opioids will suppress movement to skin incision in the presence of very low concentrations of volatile anesthetic (4). Therefore, it appears appropriate to consider the anesthetic state as being composed of an element of unconsciousness, which we will call hypnosis, as well as analgesia and reflex suppression.

Apart from movement to noxious stimulation, we generally consider elements of autonomic response (hypertension, tachycardia, lacrimation, and diaphoresis) to be signs of inadequate anesthesia. Although these may be elements of inadequate anesthesia, we have no way of relating alterations in autonomic function directly to a measure of anesthetic state. The only absolute measure of inadequate anesthesia that we have—patient recall after surgery—is often not associated with hypertension or tachycardia (5). Recent advances in technology have resulted in various electroencephalographically derived methods of measuring the depth of anesthesia.

Utility of Depth of Anesthesia Monitoring

In the absence of a gold standard for a measure of depth of anesthesia, it is useful to consider what utility a direct measure of anesthetic depth (or hypnosis) should bring us. An effective measure of depth of anesthesia should have the following components:

- Should have a rational dose-response relationship and be independent of anesthetic used.
- Should reflect the anesthetic state during the induction and recovery in the same manner.
- Should give a measure of potential awareness.
- Should prevent relative overdosage.
- Should prevent relative underdosage.
- Should warn of equipment failure.

If our measure of anesthetic depth reduces the frequency of relative overdosage and underdosage of anesthetic, it is likely that patient recovery will be improved. It should be emphasized that currently available technologies monitor the anesthetic state at

the time of measurement and are not predictors of anything that is about to happen. For instance, if a patient demonstrates an adequate reading on an anesthetic depth monitor and the level of surgical stimulation changes, that reading may be inadequate 30 s later.

Auditory Evoked Responses

Several studies have suggested that auditory stimuli can be perceived intraoperatively and that the auditory evoked response may provide a useful monitor of anesthetic effect (6). To obtain an auditory evoked response, a sound stimulus (such as a click) is presented to the patient, and the resultant electroencephalogram (EEG) is recorded. The EEG resulting from this stimulus is of low voltage, and signal-averaging techniques are necessary to obtain an evoked response. If a repeated auditory stimulus is replied and the resultant EEG is averaged during the interval immediately after the stimulus, the non-stimulus-related portion of the background EEG may be eliminated and the specific evoked response remains (7). The auditory evoked response is divided into different segments according to the anatomic area of origin. The brainstem response occurs in the first 8 ms after the stimulus and is relatively resistant to the effects of anesthetic. The middle-latency auditory response occurs between 10 and 100 ms after stimulation, and it is the amplitude and latency of this middle-latency response that is used to measure the effects of anesthesia on the nervous system (7). Various studies have demonstrated an effective dose-response relationship with increasing concentrations of anesthesia resulting in decreased amplitude and increased latency of the resulting evoked response. This has been demonstrated for inhaled anesthetics (8,9) as well as IV anesthetics (10,11). An association has also been demonstrated (in patients undergoing cardiac surgery) between high-amplitude auditory response wave forms and implicit memory function (6).

The auditory evoked response has also been associated with return of consciousness during anesthesia (12). In this study, the isolated forearm technique was used to identify return of consciousness. Return of consciousness was seen when the latency of the potential was 44.5 ms or less. This may be a threshold above which consciousness may be expected to occur.

Peak identification and amplitude measurement of the auditory evoked response are sometimes problematic. Automated techniques that use a moving average make it possible to add the most recent epochs of data at the expense of the oldest epochs. A numerical index representing the features of the auditory evoked response relating to anesthetic depth has been proposed (13). This computes the average double differential of the wave form appearing in the time window from 20 to 80 ms after each stimulus. However, this index, which was first proposed in 1989, has not been validated in any prospective manner. Another auditory evoked response index (the sum of the square root of the absolute difference between every two successive segments of the wave form) has been described and used for a closed-loop controller (14). Although this index has been used as the input signal for a closed-loop controller, it has not been subjected to extensive validation. The validation that would be required for such an index would include demonstrating all the features of a measure of anesthetic effect described earlier. In particular, graded dose-response relationships for changing anesthetic concentrations (independent of anesthetic used) have not been demonstrated. However, the auditory evoked response does appear to change during transition from consciousness to unconsciousness.

Another auditory evoked response that may be useful in predicting wakefulness is the 40-Hz response (15,16). It is possible that the oscillations that occur at 40 Hz and are imbedded in the auditory response are attenuated by unconsciousness. Another approach is to provide the stimulus at 40 Hz (17), which produces a sinusoidal steady-state response. This steady-state response may also be a sensitive indicator of the effects of general anesthetics.

Although auditory evoked responses and their effects on anesthesia have been studied for nearly 20 yr, there is no commercially available monitor that uses this technology.

EEG Bispectrum

Because general anesthetics suppress consciousness by depressing the central nervous system, and we can measure cerebral electrical activity by the EEG, it is not unreasonable to believe that some component of the EEG should relate to the effects of anesthesia on the central nervous system. Indeed, such a relationship was first suggested in 1937 (18). Various computer-processed EEG derivatives, such as power spectral edge, median frequency, zero crossing frequency, etc., were described as potential measures of anesthetic effect on the central nervous system (19–22). However, these measures were found to be anesthetic specific and were not monotonically related to drug effect or clinical response.

The previous generation of EEG measures used a fast Fourier transformation to produce information about power and frequency. Bispectral index (BIS) represents a different descriptor of the EEG in that interfrequency phase relationships are measured. Details of the computation of bispectrum can be found in Sigl and Chamoun (23) and in Rampil (24). The development and clinical application of BIS technology has

been reviewed by Johansen and Sebel (25). Data contained in both bispectral analysis and in conventional frequency/power analysis of the EEG are used to create a proprietary variable—BIS—which measures the hypnotic component of the anesthetic state. BIS is a dimensionless number scaled from 100 to 0, with 100 representing an awake EEG and 0 complete electrical silence (Fig. 1).

The BIS scale described above was based on data obtained in volunteers to establish the relationship between BIS plasma drug concentration and level of sedation (26). The relationship between BIS, clinical sedation end points, and memory function was evaluated by using propofol, midazolam, isoflurane, or alfentanil. BIS correlated better than measured drug concentration with the observer's assessment of awareness or sedation. BIS also had a very high prediction probability for correctly identifying loss of consciousness. The 50% effective concentration (ED_{50}) for unconsciousness in volunteers was found to occur at a BIS of 67.

The ED_{50} for unconsciousness was confirmed in paralyzed patients anesthetized with thiopental or propofol (27). Patients received a single dose of thiopental or propofol and were paralyzed with vecuronium. The forearm was isolated from the neuromuscular blocking drug using a tourniquet which was inflated to above systolic pressure. The return of consciousness was defined by the patient squeezing an investigator's hand twice to command. In this study, no patient recovered consciousness with a BIS <58. A BIS of 65 signified a $<5\%$ probability of return of consciousness within 50 s.

The relationship between BIS and memory function has been assessed by Lubke et al. (28). Acute trauma patients were studied in whom BIS values varied from 20 to 90. Memory was tested by stem completion of intraoperative represented words. There was no evidence of explicit awareness. However, there was a clear relationship between BIS and the ability of patients to complete the word stems with the appropriate words heard during surgery (implicit memory). This means that patients were more likely to actually complete word stems at higher BIS values than at lower BIS values.

It has been suggested that use of BIS to guide anesthetic administration would result in reduced anesthetic dosages and an increased incidence of awareness. This does not appear to be the case. The incidence of awareness during elective general anesthesia has been reported to vary from 0.18% (29) to 0.4% (30). To date, there have been at least 1,000,000 uses of BIS, and the incidence of awareness that has been reported to the manufacturers is 0.003% (35 cases) (P. Manberg, Aspect Medical Systems, Newton, MA, personal communication). Of those 35 cases, BIS was 65 or above in 17 cases. In the other 18 cases, data were considered inconclusive either because of a lack of BIS recording or inconsistent descriptions or timing of events.

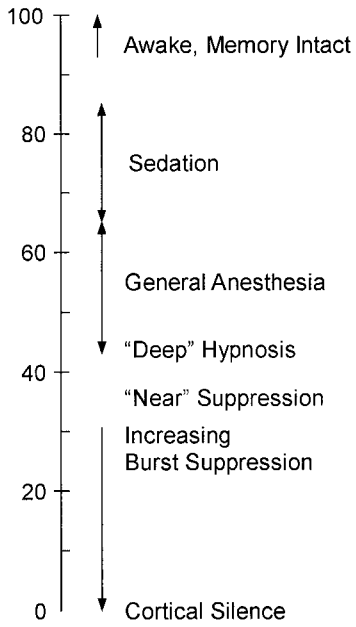

Figure 1. Bispectral index (BIS).

Although to date, we must depend on anecdotal reporting to assess the incidence of awareness during BIS monitoring, and we must also accept the possibility that there is some underreporting, it is obvious that the incidence of awareness during anesthesia with BIS monitoring has not increased above normally accepted values. In fact, it may be very much decreased, although this contention requires scientific proof.

If BIS is an effective measure of anesthetic effect, using BIS to guide anesthetic administration should allow optimization of drug delivery to each individual patient and thus prevent underdosage and overdosage of the hypnotic medications. Prevention of relative hypnotic overdose should theoretically speed emergence in recovery.

By using BIS monitoring to guide anesthetic administration, it has been demonstrated in a randomized, controlled, blinded, multicenter study with propofol/alfentanil/N_2O anesthesia that recovery is, indeed, improved (31). By using BIS to guide anesthetic delivery, the propofol infusion rate required for maintenance of anesthesia was decreased. Time to extubation was decreased, and the percentage of patients fully orientated on arrival in the postanesthetic care unit was significantly increased. Other studies have demonstrated that BIS monitoring results in reduced anesthetic requirements and improved recovery (32–35).

On the basis of the demonstrated efficacy of BIS monitoring in prospective randomized trials, Johansen et al. (36) investigated the large-scale implementation of BIS monitoring in a teaching institution.

Table 1. BIS-Guided Anesthetic Management

Intraoperative response	BIS	Treatment[a]
Increased BP and HR, autonomic or somatic response		increase hypnotic, increase analgesic, identify strong stimuli
stable	>65	rule out artifact, then increase hypnotic
Hypotension/unstable		support BP, decrease analgesic, consider amnestic
Increased BP and HR, autonomic or somatic response		increase analgesic, maintain hypnotic, add antihypertensive, or add NMB
stable	50–65	titration target, maintain vigilance
Hypotension/unstable		support BP, decrease analgesic
Increased BP and HR, autonomic or somatic response		decrease hypnotic, increase analgesic, add antihypertensive
stable	<50	decrease hypnotic or decrease analgesic
Hypotension/unstable		support BP, decrease hypnotic, and decrease analgesic

BP = blood pressure; HR = heart rate; NMB = neuromuscular blocking agent; BIS = bispectral index.
[a] Artifact refers to interference from other electrical sources and electromygraphic activity.

No particular anesthetic regimes were required. However, a decision matrix was developed (Table 1), and anesthesia personnel were instructed to guide anesthetic administration according to this decision matrix. In comparison with historical controls, less anesthetic was used when BIS monitoring was instituted. Similarly, in comparison with the historical controls, recovery times were improved, as was the incidence of patients requiring postoperative ventilatory support.

Although BIS was developed with adult EEGs, Denman et al. (37) have studied its use in pediatric patients. They found that there was an approximately linear relationship between BIS and end-tidal sevoflurane concentration in infants and children. A clinical utility trial has been undertaken in children (38) and demonstrated similar improvements in recovery to those seen by Gan et al. (31) in adults.

As with most monitoring technologies, BIS does not work perfectly in all situations. It cannot be used during ketamine anesthesia. Sedative concentrations in nitrous oxide do not appear to affect BIS (consistent with its use as a hypnotic index) (39). Electromyographic (EMG) activity may be present in unparalyzed patients, interfere with EEG signal acquisition, and contaminate the BIS calculation. This EMG activity may be interpreted as high-frequency, low-amplitude waves falsely elevating BIS. Further electrode development is under way that should reduce the possibility of EMG contamination of EEG signal (N. Chamoun, Aspect Medical Systems, Newton, MA, personal communication). Although BIS monitoring has some limited use in the intensive care situation, reducing EMG contamination of the signal should improve its utility in this setting.

Of all the EEG measures available to assess the effect of anesthesia on the central nervous system, BIS is the best validated in terms of peer-reviewed published literature. There is an alternative device, the Patient State Analyzer, manufactured by Physiometrix, North Billerica, MA. This currently has a startling lack of peer-reviewed scientific publications supporting its use. Another EEG measure that may be useful in assessing effect of anesthesia is the approximate entropy of the EEG (40).

To return to the question posed in the title of this article (can we monitor depth of anesthesia?), it is my opinion that BIS monitoring is an effective measure of anesthetic depth. It is well validated in the scientific literature and has achieved a measure of acceptance among anesthesiologists. Auditory evoked potentials may prove effective (there is certainly good supporting literature); however, the technology has not been commercially implemented. Whether the Patient State Analyzer or approximate entropy are useful measures of anesthetic effect remains to be seen.

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