Monitoring for Unconsciousness During General Anaesthesia

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Reliable monitoring of unconsciousness during general anaesthesia has been termed the “Holy Grail” of anaesthetic monitoring.1 The aim of this article is to briefly describe recent developments in this area and to critically review the current knowledge of available monitors with respect to prevention of awareness during general anaesthesia.

Awareness During General Anaesthesia

There is no generally accepted definition of awareness under anaesthesia. The term could be considered an oxymoron, given that unconsciousness is an essential feature of the state of general anaesthesia. Awareness, therefore, represents a failure to ensure absence of sensibility during general anaesthesia. An episode of awareness may or may not be associated with recall of the intraoperative event.

The consequences of awareness are variable. In the worst cases, patients suffer extreme fear, excruciating pain and overhear offensive or frightening remarks. Continuing with the worst-case scenario, they receive unsympathetic reactions from hospital staff, are not believed or have the experience trivialised, and may come to doubt their own sanity. They go on to suffer post-traumatic stress disorder with anxiety, depression and flashbacks. Not surprisingly, they may be extremely apprehensive about any future surgery. A disturbing series of case reports by Cobcroft and Forsdick make useful reading as an illustration of the devastating impacts of awareness.2 At the opposite extreme, patients who do not experience pain may be euphoric from the anaesthetic agents despite their inadequate doses and, although experiencing awareness, may rate their anaesthetic care as entirely satisfactory.3

Recent estimates of the prevalence of awareness with recall vary between 0.1% and 1% of general anaesthetics, depending on the patient group. Practising anaesthetists tend to find these figures surprising; probably because most cases do not come to attention unless patients are specifically questioned postoperatively. Myles et al reported a large study in an Australian hospital in the 1990s that confirmed an incidence of over 0.1%.4 In a prospective study designed to maximise the chance of detecting awareness with recall, Sandin et al reported an incidence of 0.18% in patients given neuromuscular blocking drugs and 0.1% in non-paralysed patients. The episodes of awareness in non-paralysed patients were reported as being brief and without sequelae.5 A follow-up study, two years after the episodes of awareness, confirmed that
post-traumatic stress disorder is common after intraoperative awareness and that severe symptoms are confined to patients who received neuromuscular blocking drugs.6

Current trends in anaesthetic practice aimed at reducing times to emergence and, in day-surgery patients, hastening discharge could potentially increase the risk of awareness. For example, use of newer drugs with a more rapid offset of action (e.g. sevoflurane, desflurane and remifentanil) would be expected to speed the return of consciousness if there is an inadvertent interruption to drug-delivery. Hence, there may be a reduced window of opportunity for detecting a technical problem before awareness occurs. Also, the aim of speeding emergence creates a pressure to titrate anaesthetic drug doses to the minimum required for each patient. Without a method to determine with certainty that a paralysed patient is unconscious, reducing doses of anaesthetic agents could increase the risk of awareness.

Monitoring General Anaesthesia

The Ideal Monitor

There are fundamental problems in attempting to monitor for unconsciousness during anaesthesia. In contrast to the physiological variables routinely monitored during anaesthesia, there is not even a generally accepted definition of consciousness. Furthermore, we have virtually no concept of how conscious experience arises. An ideal monitor of general anaesthesia would directly detect the presence or absence of this thing called “consciousness” but, given the lack of knowledge of the physiological basis of consciousness, it seems improbable that such a monitor will be developed soon.

Recent developments in monitoring the central nervous system effects of general anaesthetic agents have not been derived from any particular hypothesis regarding the origin of consciousness. Nor are they based on any particular theory of the mechanism of action of general anaesthetic agents. Without an understanding of the mechanism of consciousness, the best we can hope for at this time is a measurement that correlates with consciousness. Research has focused on attempts to correlate the state of consciousness with:

1. various features of the surface electroencephalogram (EEG); or,
2. changes in cortical auditory evoked potentials (AEPs).

An ideal monitor would detect the presence or absence of consciousness in all circumstances. It would be independent of factors that could alter the EEG such as the choice of anaesthetic agent, age of the patient, body temperature, neurological disease and psychotropic medications. If a monitor is to be used to reduce the risk of a rare event such as awareness, it must have a very high sensitivity for consciousness. Ideally, there should be no overlap in the output of the monitor in conscious individuals with the output in unconscious individuals; i.e. there should be 100% sensitivity and specificity.

Bispectral Index

The bispectral index, BIS® (Aspect Medical Systems, Natick, USA), was the first of the new generation monitors of anaesthetic effect to be commercially released and is the most extensively studied and will therefore be the main focus of this review. Rampil has given a description of the development and derivation of the BIS.7 The BIS is a score derived from the frontal EEG. The proprietary algorithm to determine this
score was developed empirically by a computer-aided search for statistical correlations between EEG characteristics and the state of consciousness. Hundreds of EEG recordings were collected from healthy volunteers during graded sedation/anaesthesia and various features of the EEG were examined for correlation with the clinical assessment of sedation. Several features of the EEG were identified and these features are fed into the BIS algorithm to derive the index. The unique feature of the BIS is that it includes analysis of the bicoherence of the EEG, which is a measure of the phase relationships between the component waves.

The output of the BIS algorithm is a score between 0 and 100. The BIS score is above 90 in awake subjects and falls with increasing sedation until the patient becomes unresponsive — usually around an index of 70. Once consciousness is lost, the BIS continues to fall with increasing doses of anaesthetic agent. The manufacturers of the BIS recommend that for surgical anaesthesia, doses of anaesthetic drugs be adjusted to maintain a BIS between 40 and 60. The BIS monitor responds appropriately to most anaesthetic drugs including volatile agents, propofol, thiopentone and benzodiazepines. There are two notable exceptions: the BIS does not appear to track the anaesthetic effects of nitrous oxide or ketamine. Also, the BIS has been reported to correlate poorly with loss of responsiveness during induction of anaesthesia with fentanyl.

To smooth out the number, the BIS is calculated as a rolling average of the previous 15 or 30 seconds of EEG recording. The index reflects the state of the EEG over the immediately preceding time period so, when the state of arousal changes suddenly, the index necessarily lags behind. When a patient responds to a stimulus, for example by movement or eye opening, it is common for the BIS to rise rapidly a few seconds after the clinical response.

The BIS monitor incorporates sophisticated and quite effective algorithms for detecting artefacts. Some types of artefact (electrocardiograph and blink artefacts) can be “repaired” but high frequency artefact from facial muscle activity or from diathermy causes rejection of the EEG epoch. During prolonged periods of diathermy, the monitor cannot calculate a BIS score. Occasionally, the algorithm fails to reject high frequency artefact, resulting in a falsely high BIS. The latest revision of the BIS monitor (BIS-XP) is much more resistant to high frequency artefact. This should reduce the problems of falsely high readings and loss of readings during diathermy.

Drummond has noted that the published information regarding the reliability of the BIS is limited as most studies have been on healthy young adults receiving only one or two drugs. In contrast to highly controlled studies, real-world patients receive a multitude of different combinations of anaesthetic drugs. The reliability of the BIS in patients on psychotropic medications and patients with central nervous system diseases has not been established. With regards to elderly patients, Katoh et al studied the BIS scores at low doses of sevoflurane and compared patients over 65 years with younger adults. They found that the BIS performed similarly well in predicting loss of consciousness in each of the age groups studied. However, there is a phenomenon in elderly patients whereby the EEG displays increased high frequency activity just prior to the onset of burst-suppression and this can cause a paradoxical increase in the BIS with increasing doses of anaesthetic agent.

Memory, Recall and the BIS

If a subject is presented with information while being sedated with anaesthetic
agents, the chance of them recalling the information has been shown to correlate well with the BIS. Glass et al investigated a variety of anaesthetic agents and calculated that the chance of remembering a picture or a word was less than 5% if the BIS was below 64 at the time of the stimulus. In the year 2001, the manufacturer of the BIS claimed that the monitor had been used on over 2 million patients and that they had received 54 reports of possible awareness occurring while the patients were monitored with the BIS. In 28 of these cases, the trend recording of the BIS could be retrieved and in each of those cases the index was over 65 at the time of awareness. The latest information from the manufacturer is that BIS monitoring has been used in over 5.5 million cases and, at the time of writing, there has yet to be reported a definite case of intraoperative awareness with a trend record confirming a BIS below 60 at the time of the event.

It is now well known that doses of anaesthetic agents adequate to prevent explicit recall of events do not always suppress all evidence of learning. Implicit memory is said to occur if a stimulus presented during an anaesthetic, whilst not consciously recalled, is found to alter subsequent behaviour. In a study of implicit memory formation during general anaesthesia for trauma surgery, the likelihood of implicit memory correlated well with the BIS, but not with other indicators of anaesthetic effect such as spectral edge frequency, end-tidal volatile concentration, or haemodynamic variables. In that study, there was still some evidence of implicit memory formation at BIS scores below 60 (but no incidents of explicit recall).

**Consciousness, Responsiveness and the BIS**

Sedation can be graded according to the strength of the stimulus required to elicit a response and the BIS has repeatedly been shown to correlate well with such a grading. However, the correlation is not absolute as there is always some overlap between the BIS scores of responsive versus non-responsive individuals. That is, there is no cut-off BIS value that enables detection of consciousness with both 100% specificity and 100% sensitivity.

The BIS is influenced by both the dose of anaesthetic drugs and the intensity of surgical stimulation. This means that, prior to the onset of surgery, it is not possible to use the BIS to determine if the dose of anaesthetic agent is appropriate. Röpcke et al found the average desflurane concentration required to achieve a BIS of 50 in healthy adults prior to skin incision was 2.2%, compared to 6.8% during laparotomy. It is common to see the BIS rise suddenly after a stimulus such as incision or intubation. The change in BIS after stimulation is unpredictable and can be obtunded by prior administration of opioids. The BIS gives information about the current state of the EEG — or, more accurately, the average state of the EEG over the preceding 15 or 30 seconds — but does not reliably predict the future response of a patient to a new stimulus. If general anaesthesia is defined as a state of unrousable unconsciousness, it could be said that the BIS correlates well with the state of unconsciousness, but correlates less well with the unrousability.

**Use of BIS monitoring to individualise anaesthetic dose**

With both intravenous and inhalational anaesthetic agents, there is significant variation between individuals in the dose required to achieve unconsciousness. A common approach to this problem, particularly in paralysed patients, is to administer
a dose that the anaesthetist judges will be adequate to prevent awareness in the vast majority of patients. The problem with this approach is that most patients receive a dose in excess of their requirement, sometimes resulting in untoward side effects and delayed emergence. The potential advantages of a monitor that could facilitate individualised dosing are obvious. By titrating anaesthetic administration to the BIS, both the average doses of anaesthetic drugs and the time to emergence can be reduced.\textsuperscript{21} The cost savings could be significant, although in one report the drug and time savings were unimpressive.\textsuperscript{22}

Monitoring the cortical effect of general anaesthetic agents has the potential to enable more rational treatment of haemodynamic disturbances. For example, if the blood pressure rises above acceptable limits, BIS monitoring may help resolve the dilemma of whether or not to increase the dose of hypnotic agents. If the BIS is already below 50, inadequate anaesthesia is highly unlikely and it may be more appropriate to administer opioids or antihypertensive drugs. Conversely, with hypotension the BIS monitor may be used to confirm that the patient requires lower than average doses of anaesthetic agents. On the other hand, if the hypotensive patient has a BIS above 60 it would not be advisable to reduce anaesthetic doses and pharmacological support of the cardiovascular system may be more appropriate.

\textit{Does the BIS reduce the risk of awareness?}

The low prevalence of awareness under general anaesthesia creates great difficulties in finding a definitive answer to this question.\textsuperscript{23} A randomised trial would require a prohibitively large number of patients to detect a clinically significant reduction in the incidence of awareness in all patients having general anaesthesia. To deal with this problem, a multicentre randomised trial currently underway in Australasia (the “B-Aware Trial”) is confined to patients thought to be at higher risk of awareness. There are also two larger non-randomised prospective studies in progress internationally (one cohort study and one historically controlled) which will attempt to document the incidence of awareness in the presence of BIS monitoring.

The BIS monitor appears to track the effect of anaesthetic agents reliably in the vast majority of cases so that a failure of drug delivery (e.g. faulty vapouriser or propofol pump) should lead to an unexpectedly high BIS. Hopefully, this would alert the clinician before awareness occurs.

\textit{Could Using the BIS Monitor Cause Awareness?}

The theoretical concern that use of the BIS monitor could increase the risk of awareness must be considered. As noted above, potential advantages of using the BIS to titrate anaesthetic doses include more rapid and predictable emergence times, reduced side effects of anaesthetic drugs and reduced drug costs. However, with regard to the risk of awareness, any strategy aimed at reducing anaesthetic agent dosage must be examined very carefully, as there is clearly an inherent tension between the two goals of preventing awareness and reducing drug use. If a monitor is used to guide a reduction of anaesthetic dosage to the bare minimum in every patient, then the risk of awareness could be increased. If anaesthetic doses are adjusted to maintain patients’ BIS scores close to a certain value, then it is important that the chosen BIS value represents an extremely low probability of consciousness.

The recommended target for the BIS during surgery is between 40 and 60, but scores approaching 60 may in fact represent a very narrow safety margin in some patients. In
the study by Flaishon et al, two out of 40 patients obeyed commands at BIS scores of 58 or 59. Kearse et al reported responses to voice with BIS scores down to 57 and inspection of the of data in other studies indicate that some subjects responded to voice at BIS scores less than 60 and as low 54. It is important to note that the BIS scores in these studies were recorded prior to any stimulation. With arousal, the EEG changes and the BIS subsequently rises (the BIS necessarily lags behind the cortical changes). Utilising the isolated forearm test, Schneider et al found that some patients responded to command after the stimulus of tracheal intubation, despite a BIS below 60 prior to the stimulus. The BIS scores rose to between 65 and 80 in those patients who responded (none of whom had any recall). These data indicate that BIS scores approaching 60, particularly if there is no stimulation at the time, can be associated with inadequate anaesthesia and a new stimulus, such as intubation or surgical incision, may then cause return of consciousness. Therefore, the use of BIS monitoring does not replace the clinical skill of the anaesthetist in anticipating the likely effects of intense stimulation and administering adequate drug doses in advance to prevent awareness. Use of BIS monitoring without bearing in mind the above considerations could be falsely reassuring and could theoretically contribute to cases of awareness.

It is important to note that the above speculations about the possibility of BIS monitoring leading to awareness are entirely theoretical. Although it is known that cases of awareness have occurred in the presence of BIS monitoring, details of most of these cases have not been published so it is not possible to say whether BIS monitoring could have contributed to the problem. If use of BIS monitoring to guide anaesthetic doses can lead to awareness, it would only take one or two cases per thousand for this effect to override any potential benefit of the monitor in detecting awareness.

**Movement**

The issue of unwanted patient movement is interesting. When the BIS algorithm was developed, it was hoped that it would predict movement in response to surgical stimuli. This did not succeed and the focus switched to the BIS as an indicator of the hypnotic effect of general anaesthetics. Suppression of movement by anaesthetic agents probably occurs at the level of the spinal cord, so it is perhaps not surprising that a monitor of cortical activity fails to predict movement. Administration of opioids during a general anaesthetic has little effect on the EEG, and therefore the BIS, but significantly reduces the likelihood of movement on skin incision. Guignard et al found that giving remifentanil prior to intubation in patients anaesthetised with propofol had no immediate effect on the BIS but there was a dose-dependent inhibition of both the rise in BIS after intubation and the likelihood of movement after intubation.

If a monitor could be used to guarantee immobility without giving muscle relaxants, the number of patients being paralysed could be reduced and, presumably, the risk of awareness reduced in some patients. However, if the BIS is used to minimise the dose of anaesthetic agents, this can lead to an increased incidence of unwanted movement, particularly if little intraoperative opioid is given. The response of the anaesthetist could be to paralyse patients whom they would not have felt obliged to paralyse at a higher anaesthetic dose. This combination — reduced anaesthetic dose and increased use of muscle relaxants — could cause awareness if using the BIS monitor failed to ensure unconsciousness.
Other monitors of awareness

Besides the BIS, the most extensively described monitor for consciousness is middle-latency auditory evoked potentials (mlAEPs). Headphones placed on the patient produce an auditory stimulus and the cortical EEG response is recorded. The term “latency” refers to the time lag between the auditory stimulus and the subsequent EEG response. Loss of consciousness with anaesthesia is associated with both an increased latency and decreased amplitude of the mlAEPs (the earlier brainstem potentials are preserved). A single number, the auditory evoked potential index, has been developed that reflects both latency and amplitude changes. A monitor (A-Line®, DanmeterA/S, Odense, Denmark) is now commercially available; this incorporates a new method of extracting the auditory evoked potential which reduces the number of stimuli required to update the index and hence improves the response time to changes in arousal. Struys et al compared this monitor to the BIS during administration of propofol as a sole agent and found it performs similarly well in distinguishing between conscious and unconscious subjects. Both monitors showed a similar overlap in their output between conscious and unconscious subjects and therefore had similar sensitivity and specificity. They also noted that both the A-Line and the BIS were similarly poor at predicting response to a noxious stimulus.

Other EEG-derived indexes are in the process of development but at this stage there is no peer-reviewed information available regarding their performance. These include monitors that calculate the entropy of the EEG signal: with the onset of anaesthesia the EEG becomes more “organised” and therefore has reduced entropy.

Could a monitor ever eliminate awareness under anaesthesia?

Some instances of awareness may not be preventable despite the aid of a monitor of consciousness. For example:

- Awareness is more common in severely hypovolaemic trauma victims and other cardiovasicularly unstable patients due to a deliberate reduction in anaesthetic dose. Even with a monitor warning of awareness, it will not always be possible to give adequate anaesthesia.
- Awareness due to the accidental administration of muscle relaxant prior to induction of anaesthesia would not be prevented by monitoring.
- Intraoperative monitoring would not be expected to prevent spurious reports of awareness. Human memory is never entirely reliable and could be even less so with the emotional stress of surgery, along with the effects of illness and anaesthetic drugs. Awareness is unequivocal if the patient can relate explicit details of intraoperative events that they could not have known about without having been conscious at the time. However, the experience described by the patient is often less clear-cut, making it difficult to be certain whether true intraoperative awareness occurred. Experiences during the early recovery period, either real or dreamt, can be remembered by the patient as having occurred intraoperatively. Also, it is conceivable that the rare patient might fabricate a report of awareness.
- Even if a monitor indicates possible consciousness, the response of the anaesthetist may not always prevent recall. For example, two cases have been reported of awareness despite the BIS monitor warning of inadequate anaesthesia. In the first case, the anaesthetist increased the propofol dose but it was only later discovered that the propofol infusion was not reaching the patient. In the second case, there was a technical failure in the delivery of volatile agent. The BIS was only moderately
raised (65-70) and the anaesthetists, believing this to be acceptable, did not discover the technical problem for some time.

Conclusions
The BIS and other more recently developed monitors offer the possibility of rational administration of agents aimed separately at suppressing consciousness and suppressing reflex responses to surgical stimuli. Use of the BIS has been found to reduce average anaesthetic drug use and reduce times to emergence. However, the BIS is not an ideal monitor, as it does not perform equally well for all anaesthetic agents and there is some overlap between the index in conscious and unconscious patients. A BIS within the recommended range is not an absolute guarantee of adequate anaesthesia as the index can increase suddenly and unpredictably with a new stimulus. It remains to be demonstrated whether use of the BIS, or any other monitor, reduces the risk of awareness under anaesthesia and there remains a theoretical possibility that it could have the opposite effect.

References
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