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Depth of anaesthesia monitoring: what's available, what's validated and what's next?

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Depth of anaesthesia monitors might help to individualize anaesthesia by permitting accurate drug administration against the measured state of arousal of the patient. In addition, the avoidance of awareness or excessive anaesthetic depth might result in improved patient outcomes. Various depth of anaesthesia monitors based on processed analysis of the EEG or mid-latency auditory-evoked potentials are commercially available as surrogate measures of anaesthetic drug effect. However, not all of them are validated to the same extent.

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New surgical procedures, increasing prevalence of day surgery and pressure to deliver 'value for money' all influence the choice of drugs and techniques for anaesthesia. Advanced monitoring of drug effect might help to optimize quality of drug delivery, possibly reduce costs and improve patient outcomes.

Anaesthesia is a balance between the amount of anaesthetic drug(s) administered and the state of arousal of the patient. Given that the intensity of surgical stimulation varies throughout surgery, and the haemodynamic effects of the anaesthetic drugs may limit the amount that can be given safely, it is not uncommon for there to be critical imbalances between anaesthetic requirement and anaesthetic drug administration. Underdosing may be because of equipment failure or error may occur.[14 46] Conversely, inappropriate titration of the hypnotic components, leading to an excessive depth of anaesthesia (DoA), might compromise patient outcome.[39]

Patient movement in response to noxious stimulation remains an important sign of inadequate DoA, but is unreliable[53] and is suppressed by paralysis. Traditional clinical signs such as hypertension, tachycardia and lacrimation are unreliable indicators of DoA.[62 78] A reliable DoA monitor is keenly sought[69] and several methods have been developed. Early techniques based on real time signal processing such as the raw or summated EEG, and lower oesophageal contractility, were unreliable. The isolated forearm technique has had some enthusiasts,[51 71] but it is cumbersome and

has undergone limited evaluation as a DoA monitor and has not been widely adopted; nevertheless, it remains a useful comparator in the evaluation of newer methods.[50]

Auditory-evoked potential (AEP) responses have attracted attention since studies in the 1980s demonstrated a clear dose–response with increasing anaesthetic administration reducing the AEP amplitude and increasing its latency (Fig. 1).[16 66 68]

Advances in computer power and miniaturization have allowed the concomitant development of processed electroencephalographic modalities such as bispectral index (BIS, Aspect Medical Systems, Newton, MA, USA) and Spectral Entropy (GE Healthcare, Helsinki, Finland). In the last 10 yr, there has been a dramatic increase in the number of studies reporting development and validation of DoA devices. Most current proprietary DoA machines use a dimensionless monotonic index as a measure of anaesthetic depth, typically scaled from 100 (awake state) to 0 (deep coma).

Do we need DoA monitors?

Individual accounts of awareness during surgery make grim reading and have been in the anaesthesia literature for years.[1 52] Individuals who have experienced awareness are frequently traumatized by the experience and anxious both for an explanation of what happened to them and assurances that the same will not happen to others in the future. Commercial developments in clinical monitoring now offer several devices to measure DoA and pressure
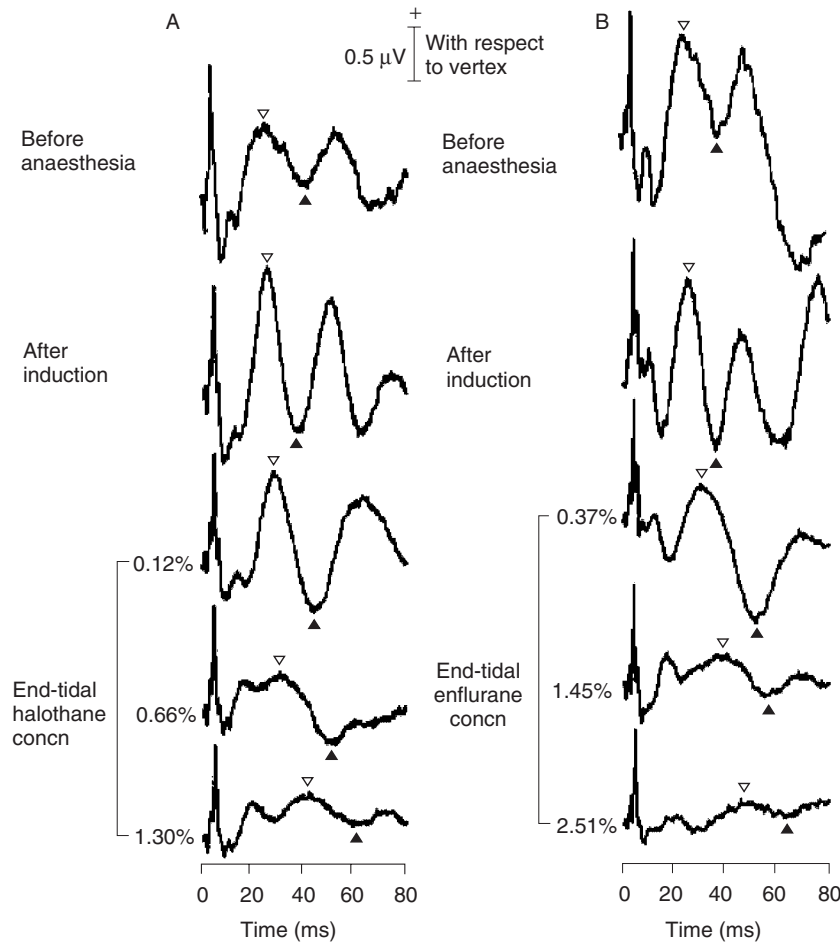
Fig 1 Averaged cortical auditory evoked responses for one subject from each group: halothane (A), enflurane (B). The traces represent responses obtained before anaesthesia, after induction, and at different end-tidal concentrations of each agent. Pa is denoted by ▲ and Nb by ▽(adapted from reference[67] with permission).

Table 1 Incidence of awareness

Author	Study period	Nature	Overall rate		Non paralysed patients	Paralysed patients	Comment
Sebel, *Anesth Analg* (2004)[56]	2001–2002	Prospective	19 575	0.13			0.36% if 'possible awareness' is included
Myles, *Br J Anaesth* (2000)[41]	1993–2000	Database review	10 811	0.11			
Sandin, *Lancet* (2000)[53]	1997–1998	Prospective	11 785	0.15	0.1	0.18	
Ekman and colleagues, *Acta Anaesthiol Scand* (2004)[18]	Pre 2003	Retrospective	7826	0.18			
Rungreungvanick, ASA abstract (2005)	2005	Retrospective	150 000	0.07			

is building to deploy this technology. Before clinicians do so we should first address key questions about awareness, DoA monitoring and patient outcomes.

What is the real incidence of awareness under anaesthesia? Published estimates are alarmingly high (Table 1).

Sebel and colleagues[56] reported a 0.13% incidence amongst 19 575 patients with risk increased by high ASA physical status score, but no effect of age and sex and others have reported rates of 0.18 and 0.11%.[53] If these figures are

correct, then very large numbers of patients experience awareness. The problem may be even greater in paediatric practice with an incidence of 0.8% reported amongst 1250 children aged 5–12 yr.[12 34] Whether this increased incidence reflects underlying physiological differences, alternative anaesthetic techniques or differential reporting remains unclear. Awareness, however, defies simple analysis and critics[17] suggest that these headline figures may be substantially inflated by memories generated during

awakening (remembrance) or in the postanaesthesia care unit or even false memories generated by repeated interviewing.

Does this debate matter, and what do anaesthetists really think is the incidence of awareness? Each case of true intraoperative awareness is a tragedy for the patient concerned, and it would be easy to state that the only acceptable incidence of awareness should be zero. However, marketed DoA monitors come with associated capital and revenue costs which might compromise alternative investments with potential outcome benefits. Anaesthetists rate awareness as only a moderate problem and although in an Australian survey more than 50% had experienced a patient with awareness, they nevertheless underestimate the overall incidence and also consider their individual incidences to be lower than average.[42]

Can DoA monitors detect awareness? When transitions between consciousness and unconsciousness were engineered in a clinical trial using either inhalational or i.v. anaesthesia, neither BIS nor patients state index (PSI) were reliably able to distinguish consciousness from unconsciousness in individual patients.[54] DoA monitoring is certainly effective at an anecdotal level, with individual accounts of monitoring alerting the anaesthetist to deficiencies in drug delivery, with associated lightening of anaesthesia.[37]

Does DoA monitoring reduce cost or improve care? Although intraoperative DoA monitoring may reduce drug consumption and accelerate early recovery, these do not automatically translate into early discharge or improved outcomes.[2 45 60 80] Concerns that using DoA monitoring to reduce anaesthetic drug administration might actually risk awareness[59] have proven ill founded. Whether these benefits translate into sufficient savings to justify the cost of the monitoring will depend on the cost and protocol structure of individual clinical facilities.

Can intraoperative DoA monitoring predict outcome from surgery? Although far less common than some other serious complications of anaesthesia and surgery, awareness remains of great concern to anaesthetists and to their patients.[11 28 38 42] Standard clinical practice is cautious and anaesthetists may err on the side of safety by administering larger than adequate drug doses in the hope of avoiding awareness. This generous approach to drug dosage may increase the risk of hypotension, delay recovery time, and has the potential to increase other complications. Thus, the possibility of awareness influences anaesthesia care of surgical patients on a daily basis. Recently, Monk and colleagues[39] identified three variables as significant independent predictors of mortality: patient co-morbidity, cumulative deep hypnotic time (BIS <45) and intraoperative systolic hypotension. Death during the first year after surgery is primarily associated with the natural history of pre-existing conditions. However, cumulative deep hypnotic time and intraoperative hypotension were also significant, independent predictors of increased

mortality. These associations suggest that intraoperative anaesthetic management may affect outcomes over longer time periods than previously appreciated.[39]

What DoA monitoring technologies are available?

Both spontaneous EEG and mid-latency auditory-evoked responses (MLAEP) offer information about the hypnotic state of the patient. As the raw waveforms are difficult to interpret, it is customary to transform the data into a single number. Several DOA monitoring devices have been developed in the past few years. Some have already been withdrawn from the market such as the EEG-derived SNAP[TM] Index (Viasys Healthcare, Madison, WI, USA) and the ARX-derived AER Index or AAI 1.5 (Danmeter A/S, Odense, Denmark) derived from the MLAEP. Others are newly introduced and require further evaluation. These include the EEG-derived cerebral state index (Cerebral State Monitor CSM, Danmeter A/S, Odense, Denmark) and the AAI 1.6 (AEP/2 monitor, Danmeter, Odense, Denmark), derived as a composite index from MLAEP and spontaneous EEG signals. The PSI (Patient State Analyser, Hospira, Lake Forest, IL, USA), based on derived quantitative EEG features in a multivariate algorithm that varies as a function of the hypnotic state,[15] is only available in the USA. Some other EEG-derived techniques, such as approximate and Shannon entropy, are not available commercially.[45] We will focus on the more established monitors which are available in Europe, which are the BIS (Bispectral Index Monitor, Aspect Medical Inc., Newton, MA, USA), the Narcotrend index (Narcotrend Monitor, Schiller AG, Baar, Switzerland) and the State and Response Entropy (SE and RE), derived from the Spectral Entropy from the EEG (M-Entropy module, GE Healthcare, Helsinki, Finland).

Technical aspects

Specific EEG sensors have been developed for DoA monitors.

For the BIS monitor, Zipprep[TM] electrodes (Aspect Medical Inc., Newton, MA, USA) have been developed to reduce skin impedance. Originally, single electrodes (Fig. 2) were developed. Now, three (standard BIS sensor) or four (BIS-XP sensor) (Fig. 2) electrodes are integrated in one sensor to obtain the electroencephalographic signal from the forehead. The M-Entropy module (GE Healthcare, Helsinki, Finland) is based on a modification of the BIS sensor. Integrated multi-electrode sensors simplify application of DoA monitoring, and provide a revenue stream for manufacturers. Sensors and cables may be 'chipped' to prevent re-use. In contrast, the Narcotrend monitor[8] works with self-adhesive pre-gelled standard ECG electrodes.

After digitization of the original analogue EEG signal, derived variables are displayed. All three monitors provide
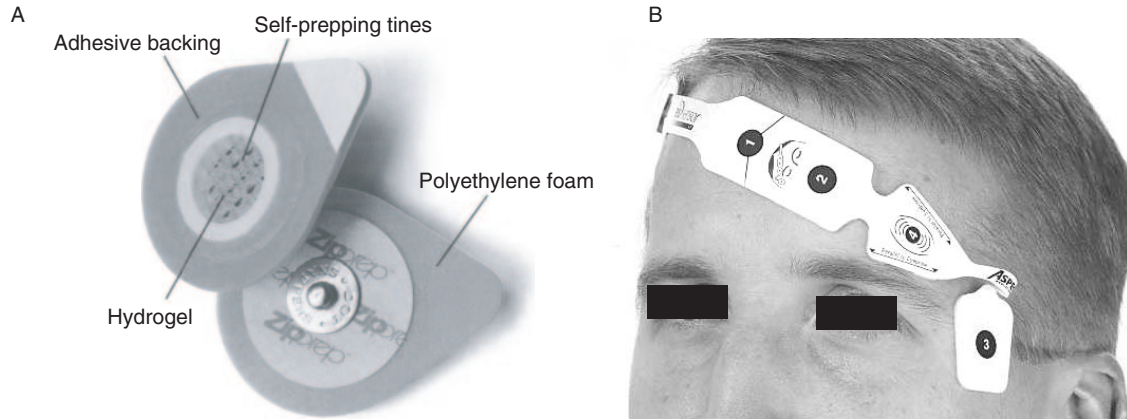
Fig 2 ZIPPREP ©EEG electrode (Aspect Medical Inc., Newton, MA, USA). (A) The original single sensor type. (B) The ZIPPREP sensor incorporating four ZIPPREP sensors.
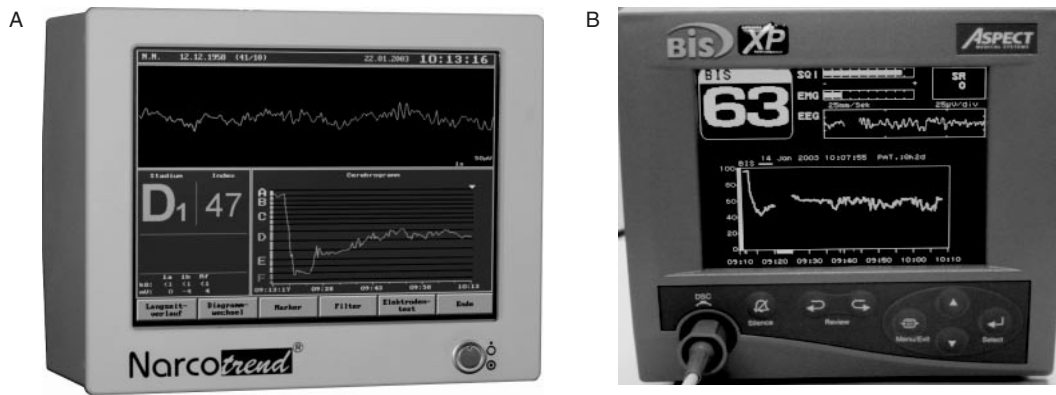

Fig 3 Frontal view of the Narcotrend Monitor (Narcotrend Monitor, Schiller AG, Baar, Switzerland) (A) and the A-2000 BIS-XP Monitor (Aspect Medical Inc., Newton, MA, USA) (B).

the raw EEG, a calculated dimensionless variable, between 0 and 100, being BIS, the Narcotrend index, and the SE and RE, respectively. All monitors show the trend of the calculated variable. Other variables displayed are: signal quality index, electromyographic activity (EMG), burst suppression ratio of the EEG (BSR) and the trend of a second variable (e.g. spectral edge frequency) for the BIS Monitor or power spectrum, impedance and Narcotrend stage classification for the Narcotrend monitor (Figs 3 and 4).

What does the DoA monitor do?

The mathematical principles and algorithms used to generate the calculated variables of the three monitors are completely different. Whereas details of the algorithms are proprietary and not published, the basic principles have been described.

(i) BIS. The fast Fourier transformation, yields a power spectrum and a phase spectrum. EEG variables, such as spectral edge frequency or median frequency, are calculated solely from the power spectrum. The phase spectrum was traditionally ignored as not being of

Fig 4 View of the M-Entropy module and the partial screen of the S5-Monitor (GE Healthcare, Helsinki, Finland).

interest. In contrast, the bispectral analysis is based on power spectrum and phase spectrum and quantifies the coupling of phase angles of different frequencies. The BIS integrates several disparate descriptors of the EEG into a single variable based on a large volume of clinical data to synthesize a combination that

correlates with behavioural assessments of sedation and hypnosis. The SynchFastSlow sub-variable is the contribution from bispectral analysis. SynchFastSlow is defined as the log of the ratio of the sum of all bispectrum peaks in the area from 0.5 to 47 Hz over the sum of the bispectrum in the area 40–47 Hz. BIS is defined as a proprietary combination of SynchFastSlow with a sub-parameter from the frequency domain ('β ratio') and a sub-variable from the time domain (burst suppression).[50]

(ii) Narcotrend index. The methods for the automatic classification of EEG were developed on the basis of its visual assessment, which originally related to sleep classification. In 1937, Loomis and colleagues[33] described systematic changes of the EEG during human sleep and defined five stages, A–E, to distinguish different EEG patterns. Subsequently, the scale was extended, refined by the definition of sub-stages, and applied to the classification of EEGs recorded during anaesthesia (stages A=awake to F=very deep level of anaesthesia).[27] Numerous quantitative features from the time and the frequency domain were extracted, for example, spectral variables, entropy measures and autoregressive variables. The extracted variables were statistically analysed to identify a subset of EEG variables that were best suited to discriminate between the different visually determined EEG sub-stages between A and F. Finally the sub-stages were further refined and transformed to a numerical index between 0 and 100.[26]

(iii) M-Entropy module. It is proposed that the EEG can be adequately described with methods from non-linear dynamics. Entropy is a mathematical concept to quantify non-linear dynamics. The concept of spectral entropy originates from a measure of information called Shannon entropy. When applied to the power spectrum of EEG, spectral entropy is obtained and measures the regularity of the frequency distribution. RE is calculated in the frequency range from 0 to 47 Hz and includes EEG and EMG activity. SE is calculated in the frequency range from 0 to 32 Hz and should mainly include EEG activity.[74 75 77]

Special features of DoA monitors

In early attempts to use on-line EEG monitoring to measure intraoperative depth of hypnosis, a simple EEG parameter such as spectral edge frequency was used.[30] The usefulness of this approach is limited by sensitivity to artifact, and paradoxical increase during light sedation in the presence of β activity and during deep anaesthesia as a result of burst suppression. To outperform these early technologies, new DOA monitors include an artifact detection algorithm and need to guarantee a monotonic dose–response relationship, even in the presence of β activity or burst suppression.

Artifact detection

The descriptions of the artifact detection algorithms are typically cryptic for all monitors. It is, however, likely that two different artifact detection algorithms are incorporated. The first artifact detection algorithm identifies specific artifacts such as electrocautery, ECG, pacemaker spikes, EMG activity or eyeblink events by exceeding a preset threshold value in a certain frequency range (spectral entropy)[77] or by cross-correlation of the EEG epoch with a template pattern (BIS).[50]

The second artifact detection algorithm is more general: if the variance of an epoch of raw EEG obtained by the BIS monitor changes markedly from an average of recent previous epochs, the new epoch is marked as 'noisy' and not processed further. However, the new variance is incorporated into an updated average. If the variance of new incoming epochs continues to be different from the previous baseline, the system will slowly adapt as the previous average changes to the new variance.[50] This is used in the Narcotrend algorithm, where 'background' variables are calculated and updated during the course of an EEG recording.[25] This approach to artifact detection is very effective, but the slow adaptation may be responsible for delayed display of new index values at the transition from 'general anaesthesia' to 'awake'.[24] As the Narcotrend algorithm is based on the classification of an EEG epoch into one of the sub-stages, a sufficient similarity of the epoch to one of the typical EEG stages is required for a classification to be made.[1] This leads to the exclusion of more EEG epochs from index value calculation for Narcotrend index than for BIS.[19]

β activation

Most sedative and anaesthetic agents produce a characteristic increase in β EEG activity between 13 and 30 Hz (Fig. 5).

To prevent this pattern of EEG activation being reported as arousal, a β activity sub-variable is included in the BIS algorithm. The 'β ratio' sub-variable is the log ratio of power in two empirically derived frequency bands: $\log[(P_{30-47}\ \mathrm{Hz})/(P_{11-20}\ \mathrm{Hz})]$. The combination algorithm that determines BIS therefore weights the β ratio most
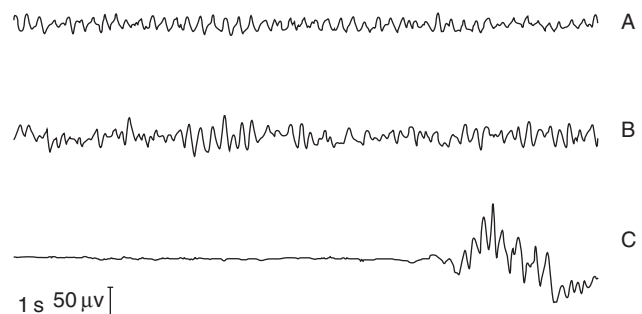

Fig 5 Raw EEG waves. A, awake state; B, β-activation; C, burst suppression.

heavily when the EEG has the characteristics of light sedation.[49] The Narcotrend algorithm classifies EEG epochs with high β activity as Narcotrend stages B_{0-2} which translates into Narcotrend index values of 80–94.[26] The Entropy module does not have a special feature for high β activity, assuming that the spectral entropy is monotonically decreasing with increasing anaesthetic drug concentrations even with β activity during light sedation.

Burst suppression

Burst suppression represents a benign pattern frequently seen in healthy brain at deep levels of anaesthesia. It can be identified in the raw EEG and is composed of episodes of electrical quiescence ('suppression') alternated with high frequency, high amplitude electrical activity ('bursts') (Fig. 4). Increasing anaesthetic drug concentration causes increased duration of the suppression periods. Burst suppression patterns of the EEG are classically quantified as BSR defined as the percentage duration of suppression/duration of the epoch.[67 75 76]

To avoid a paradoxical increase in the presence of burst suppression, the BIS includes a burst suppression sub-variable. At BSRs between 5 and 40% the BIS remains nearly unchanged. At BSRs >40%, the BIS can be calculated as $BIS=50-(BSR/2)$ for the A-1000 BIS monitor (Aspect Medical Inc., Newton, MA, USA).[67] For the A-2000 monitor (version XP) the formula changed slightly to $BIS=44.1-(BSR/2.25)$.[20] For Narcotrend, algorithms for the classification of stage F were developed that are based on the proportion and intensity of very flat electroencephalographic segments. The Narcotrend stages F_{0-1} can be translated into Narcotrend index values of 1–12. These Narcotrend index values correlated closely with the BSR calculated by the BIS monitor.[26] When burst suppression sets in, spectral entropy values RE and SE are in principle computed in the same way as they are calculated at lighter levels of hypnosis. The part of the signal that contains suppressed EEG is treated as a perfectly regular signal with zero entropy, whereas the entropy associated with the bursts is computed as usual.[75 77] The relation between SE and burst suppression could be described with a linear fit as $SE=29-(BSR/3.25)$ ($R^2=0.88$).[20]

How can we assess a DoA monitor's performance?

Validity is a measure of accuracy and this is difficult to quantify here as there is no accepted gold standard measure of anaesthetic depth. Indirect measures can be used.[3] Face validity refers to the extent to which the monitor appears to be measuring what it is intended to measure, and is a subjective judgement. For example, it is reasonable to expect a DoA monitor that derives its indices from the EEG to measure anaesthetic drug effect. Construct validity refers to the extent to which the monitor relates to theoretical concepts (constructs) of the phenomenon under study.

For example, delayed recovery time or inability to process memory should occur with deep levels of anaesthesia. Criterion (or convergent) validity is the extent to which the monitor agrees with another instrument measuring related features (such as a sedation scale or markers of cerebral activity), or anaesthetic drug concentration.

Reliability is a measure of consistency, and can be assessed by test–retest reliability: concurrent or repetitive measures of DoA will be comparable at a stable anaesthetic state. Utility can include ease of clinical use and interpretation, freedom from artifact, robustness and low cost.

Perhaps the most important function of DoA monitoring is to detect and prevent awareness. This can be quantified but because awareness is subjective and open to interpretation, it is strongly recommended that a structured questionnaire[3 43 53 56] and adjudication committee be used to verify awareness reports.[43 56]

Validation of DoA monitoring

Anaesthetic depth is a simplified construct of hypnosis, amnesia, antinociception and reflex suppression. The most widely used method to compare anaesthetic drug potencies is the concentration at which movement in response to a nociceptive stimulus is suppressed, the minimum alveolar concentration (MAC) or plasma concentration (Cp50) to prevent response in 50% of subjects. However, MAC and Cp50 reflect primarily spinal responsiveness and do not require cortical function.[48 49] In an editorial, Glass[22] stated that the interaction of hypnotics and opioids for achieving two major endpoints in general anaesthesia (loss of consciousness and inhibition of movement at skin incision) are based on the evidence that loss of consciousness and response to skin incision are not a single continuum of increasing 'anaesthetic depth' but rather are two separate phenomena. Combining these observations, Glass[22] proposed the following hypothesis of general anaesthesia. General anaesthesia is a process requiring a state of unconsciousness of the brain (produced primarily by the volatile anaesthetic or propofol). In addition, noxious stimuli need to be inhibited from reaching higher centres. This is achieved by the action of the opioid at opioid receptors within the spinal cord (or local anaesthetics on peripheral nerves, or volatile anaesthetics on the spinal cord when administered at concentrations equal to their MAC). As such, the underlying mechanisms of general anaesthesia[10] suggest that no single component of anaesthesia can be used to define overall 'depth', but for most anaesthetists patient unconsciousness and the prevention of memory formation during surgery remain key objectives. Thus, hypnotic depth is the primary endpoint of interest, and this has become the focus of contemporary DoA monitoring. DoA monitor development programmes typically include correlation studies, clinical trials of recovery times and assessment of the ability of DoA monitors to prevent

memory formation or awareness. The BIS monitor is the most widely evaluated device.

Correlation studies

There is no gold standard measure of anaesthetic depth and so indirect parameters must be used. These include anaesthetic drug concentration and, for lighter levels of anaesthesia, sedation scales. A strong correlation between a DoA index and anaesthetic drug concentration, and/or between a DoA index and deepening sedation, provides construct validity for DoA monitoring. Many such studies have been published. For example, Leslie and colleagues[29] compared measured propofol blood concentration with BIS and 95% spectral edge frequency in volunteers. The mean (SD) propofol blood concentration suppressing learning by 50% was 0.66 μg ml^{-1}. BIS decreased linearly as propofol blood concentration increased (r=0.69), but there was no significant correlation between spectral edge frequency and propofol concentration. Doi and colleagues[13] compared BIS, 95% spectral edge frequency, median frequency and AEP index in 10 patients during emergence from anaesthesia. They compared correlation of the signals with calculated blood propofol concentrations. Each of the electrophysiological variables correlated with blood concentrations of propofol: BIS, r=0.74; 95% spectral edge frequency, r=0.69; median frequency, r=0.65; and AEP, r<0.3. Interestingly, despite the poor correlation between AEP and propofol concentration, this latter study found that AEP was a good discriminator of consciousness/unconsciousness at the end of surgery.[13]

Recovery times

Randomized trials comparing DoA-guided anaesthesia with routine care (based on traditional measures such as patient age, health status, blood pressure and heart rate) provide a very good assessment of the utility of DoA monitoring, particularly when applied to large and diverse groups of patients managed by a broad range of anaesthetists in routine clinical settings.[70] Some such trials have been done, though typically in collaboration with manufacturers of the monitor under evaluation.[21 60 73] For example, in a multicentre, randomized trial, Gan and colleagues[21] enrolled 302 patients receiving a propofol–alfentanil–nitrous oxide anaesthetic guided by either routine traditional care (standard practice) or with additional BIS monitoring. BIS monitoring led to a reduction in propofol administration and earlier recovery when compared with standard practice. Other authors have demonstrated similar benefits with spectral entropy monitoring,[73] AAI 1.6 (AEP/2 monitor, Danmeter, Odense, Denmark),[78] and the Narcotrend device.[25] A meta-analysis of trials in 1383 day surgery patients found that use of BIS monitoring significantly reduced anaesthetic consumption by 19%, reduced the incidence of nausea/vomiting by 23% and reduced time in the recovery room by 4 min.[31] In contrast, there have been several trials that found no substantial effects on recovery times when using DoA monitoring.[9 47]

There are important issues raised by this series of studies. First, meaningful reductions in recovery times require a substantive reduction in anaesthetic drug administration. Second, titration of anaesthesia using very short-acting drugs, such as with desflurane, as compared with propofol, is unlikely to be meaningfully assisted by DoA monitoring because there is already a rapid recovery time.

Suppression of memory formation and/or movement in response to commands

Several studies have measured intraoperative learning or memory formation with postoperative behavioural change, word-stem completion testing or purposeful movement.[35 36 51] Lubke and co-workers[36] studied explicit and implicit memory during emergency Caesarean section with a light anaesthetic state (mean BIS=76). They were able to demonstrate intraoperative memory formation with a word-stem completion test after surgery. Russell[51] studied 12 women undergoing major gynaecological surgery and used the isolated forearm technique to validate the Narcotrend index. Only 41 of 92 (45%) responses detected by the isolated forearm technique were associated with an increase in the Narcotrend stage that would indicate consciousness. Thus the Narcotrend was unable to differentiate reliably between consciousness and unconsciousness in this setting.

Definitive studies

Several large-scale studies have been done to determine whether DoA monitoring can reduce the risk of awareness.[18 43 56] Ekman and colleagues[18] did a before-and-after comparison of the use of BIS monitoring in 4945 patients undergoing relaxant general anaesthesia with a group of 7826 patients from a previous study when no DoA monitoring was used. They found a significant 5-fold reduction in risk, 0.04% vs 0.18%, P=0.038. Myles and co-workers[43] did a randomized, double-blind, multicentre trial in 2643 adult patients at high risk of awareness. Patients were randomly assigned to BIS-guided anaesthesia or routine care. Patients were assessed by a blinded observer for awareness at 2–6 h, 24–36 h, and 30 days after surgery. An independent committee, blinded to group identity, assessed each report of awareness. There were two reports of awareness in the BIS-guided group and 11 reports in the routine care group, P=0.022. BIS-guided anaesthesia reduced the risk of awareness by 82% (95% CI: 17–98%). An observational cohort study has been done in the USA.[56] A total of 25 awareness cases were identified from 19 575 patients in seven centres (0.13% incidence). Use of DoA monitoring was not associated with a reduction in the risk of awareness, but this could not be reliably tested in this study because of the expected probability that high risk cases would be more likely to be monitored (i.e. confounding by indication).

Comparison of DoA monitors

It is difficult to compare the performance of DoA monitors by ranking their correlations with anaesthetic drug concentration or recovery times across studies, given the variability in patient populations and study conditions. However, it is necessary to use statistical tests, such as prediction probability,[57 58] logistic regression and sensitivity/specificity analysis to fully describe the accuracy of these variables. Therefore, clinical endpoints should be clearly selected[23] and a direct comparison between values of various monitors should be avoided.[9 13 44 55 62 64 74–76] For example, Nishiyama and colleagues[44] compared the usefulness of the BIS, processed EEG, and AEP in 90 women undergoing mastectomy with propofol–nitrous oxide anaesthesia. They found that BIS had the lowest skin impedance and thus most reliable signals, AEP had the least spurious out-of range values and the largest responsiveness to stimulation, and the processed EEG had the fastest recovery time after electrocautery. Vanluchene and colleagues[75] studied 10 patients receiving propofol 50 mg min^{-1} until either burst suppression greater than 80% or mean arterial pressure less than 50 mm Hg was observed. Baseline variability was lowest when using SE and RE, prediction of propofol effect site concentration was highest for BIS. The same group has compared SE and RE, to measure loss of response to verbal command and to noxious stimulus with the BIS during propofol infusion with and without remifentanil. They concluded that loss of response to verbal command was accurately detected by BIS, SE and RE, except for the 100% sensitivity level where BIS performed better. Though BIS, SE and RE were influenced by remifentanil during propofol administration, their ability to detect loss of response to verbal command remained accurate. No measure could be promoted to predict loss of response to noxious stimulus.

Vakkuri and colleagues[72] compared spectral entropy (and components of frontal EMG) with BIS in 70 patients anaesthetized with propofol, thiopental or sevoflurane. Loss of and regaining of consciousness were used to calculate sensitivity, specificity and prediction probability; each were high and similar for all indices. During regaining of consciousness the relative increase was higher with entropy when compared with BIS ($P<0.01$).

DoA monitors: what's next?

Future advances in both anaesthetic technology and pharmacology will continue to increase the overall quality of anaesthesia. DoA monitors may play an important role in this. As this equipment measures cerebral drug effect, it may be considered as an integral part of anaesthetic pharmacology. For the first time, anaesthetists are able to differentiate and measure the various anaesthetic drug effects, being hypnosis and analgesia, by specific effect monitors.[10] However, much work has still to be done.

Whether or not DoA monitoring should be used in all cases, or only those at higher risk of awareness continues to be debated. This is partly an economic decision. Because the incidence of awareness is low, most randomized trials have not been powered to detect a difference in the rates of awareness, and focused on secondary or surrogate endpoints such as recovery times and quality of recovery. Awareness should be included and reported as an outcome measure in order to allow future meta-analysis. Demonstration of effectiveness does not necessarily support widespread uptake in clinical practice. Cost–benefit analyses need to be done. For example, routine awareness monitoring with a proprietary device in most patients undergoing anaesthesia would add about £30 million to UK healthcare costs. Economic analyses should include possible savings such as a reduction in drug usage, recovery times, complications and hospital stay. Awareness can still occur in patients receiving DoA monitoring.[43 56] Whether this represents a failure of the monitoring algorithm or artifact detection, some patient conditions,[43 56] or human error[46] requires further study.

When giving hypnotic drugs during anaesthesia or sedation, the aim is to achieve and maintain adequate DoA without the risks of awareness, haemodynamic instability or respiratory depression. Large inter-individual variability is found when studying population pharmacology and it is difficult to quantify the clinical/pharmacological effect. Traditionally, most anaesthetic drugs were given using standard dosing guidelines without applying knowledge of their pharmacokinetics and dynamics to control their administration. Recently, improved understanding of pharmacokinetics and pharmacodynamics has permitted target controlled infusion for i.v. agents or end-tidal controlled inhaled administration for inhaled drugs.[65] When validated, DoA monitors can be integrated into future anaesthetic advisory and feedback systems, enlarging the existing kinetic-based administration technology towards a total coverage of the dose–response relation. By measuring the patients' individual response to a given drug dose, drug administration could be guided by a pharmacodynamic advisory system estimating the complete dose–response relationship. Additionally, closed-loop technology could be used.[32 40 61 64] Such systems might help the anaesthetist in optimizing the titration of drug administration without overshoot, controlling physiological functions and guiding monitoring variables.

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