DEPTH OF ANAESTHESIA

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Introduction

Assessment of the depth of anaesthesia is fundamental to anaesthetic practice. Prior to the use of muscle relaxants, maintaining the appropriate depth of anaesthesia was a balance between abolishing movement to pain whilst maintaining adequate respiration. With the absence of movement on incision it was safe to assume that the patient was not aware, however with the use of muscle relaxants it became necessary to be certain that the administered concentration of anaesthetic agent was adequate to prevent awareness. With the emergence of new anaesthetic techniques such as intravenous anaesthesia, the use of potent opiate analgesics, newer volatile agents and more complicated regional nerve blocks, a means of measuring depth of anaesthesia is important. What began as the continuous clinical monitoring of patients' physiological parameters evolved to include the measurement of real-time airway gas volatile agent concentration and more recently the analysis of neurophysiological parameters derived from the electroencephalogram (bispectral index and evoked potentials).

In patients who are aware during anaesthesia memory may be explicit or implicit. Explicit recall involves the memory of events and speech and may result in significant psychological sequelae. Implicit memory occurs where no recollection of events exists however patient's behaviour is modified by information given during anaesthesia. The incidence of awareness during anaesthesia with muscle relaxants is thought to be between 1:500 and 1:1000[1,2,] usually assessed by postoperative reporting and interview.

The prevention of awareness begins with scrupulous anaesthetic technique. This involves the checking of all equipment, ensuring the uninterrupted delivery of anaesthetic to patients via intact

circuits and intravenous access and the use of familiar, appropriate techniques by competent practitioners. This article discusses some of the common and developing methods used to aid the assessment of depth of anaesthesia in order to prevent intra-operative awareness.

Clinical parameters

It is essential to continuously monitor patients' respiration and autonomic parameters during anaesthesia. Measurement of heart rate and blood pressure whilst regularly assessing pupil size and the presence of sweating and lacrimation provide useful information regarding the adequacy of analgesia and depth of anaesthesia. However they must be taken into context with the surgical procedure and the anaesthetic technique, as cardiovascular parameters alone are poor predictors of the hypnotic state.[3] Tachycardia secondary to anti-cholinergic drugs like atropine make the heart rate uninterpretable and beta-adrenergic blocking drugs, opiates and regional anaesthetic techniques will obtund the sympathetic nervous system response to pain. Case reports have described cases of explicit awareness during anaesthesia, evident on electroencephalographic monitoring minutes before any significant cardiovascular changes occurred.[3]

Intravenous anaesthesia and pharmacokinetic modelling of agent concentration

The use of total intravenous anaesthesia (TIVA) is becoming more common. Unfortunately there is no equivalent of measuring end-tidal volatile agent concentration. Commercially available target-controlled infusion systems using propofol, estimate a plasma concentration using a pharmacokinetics model. However estimated blood concentrations do not correlate well with measured values due to inter-patient pharmacokinetic variability. Also the clinical effects of a particular drug concentration vary between patients.[2] A recent study has tested one of these propofol target -controlled systems in 22 patients undergoing laparoscopic cholecystectomy. When setting the target concentration at 2.5 mcg/ml measured plasma propofol concentrations ranged between 2.2 and 8.1mcg/ml. Propofol concentrations were under-predicted by a median of 60%. In addition Bispectral Index (BIS) monitoring was used to adjust propofol anaesthesia to maintain a target BIS value. The study found no correlation between measured serum propofol concentration and the corresponding BIS values 4. The accurate assessment of depth of anaesthesia during TIVA is difficult and care in preventing awareness, especially with the use of muscle relaxants, is important. Interestingly the quoted rates of awareness in studies using intravenous anaesthesia and muscle relaxants show a similar incidence to those using volatiles, (0.1-0.2%).

Isolated forearm technique

The isolated forearm technique was a method of detecting awareness during clinical practice and experimentally. A tourniquet is applied to the patient's upper arm, inflated above systolic blood pressure before the administration of muscle relaxants. Movement of the arm either spontaneously or to command indicated wakefulness, although not necessarily explicit awareness. It has been used previously as a means of detecting awareness during Caesarian section under general anaesthesia and during clinical trials assessing rates of awareness. Some would argue that response to command during surgery is a late sign when attempting to prevent awareness however not all patients responding have any recall. One study assessed response to command during deep sedation targeted using Bispectral Index monitoring of patients' EEGs. 56 patients in the study were repeatedly commanded to squeeze the observer's hand and 37 patients gave an unequivocal response at some point. Of these patients only 9 had any explicit recall of the events.[5] This demonstrates that post-operative recall and reporting by patients underestimates the incidence of wakefulness and 'near-awareness' during anaesthesia. Another study from 1986 compared an etomidate intravenous anaesthetic with nitrous oxide and fentanyl based anaesthesia. 44% of the nitrous oxide group showed signs of wakefulness whilst anaesthetised.[6] One limitation of this technique is the limited time available before patients are unable to move their arm due to tourniquet induced ischaemia.

Electroencephalographic methods

Interpreting the EEG during anaesthesia attempts to monitor the effects of anaesthetic agents in suppressing cerebral electrical activity. The EEG can be obtained with the standard 19-electrode method however this is time-consuming and impractical and requires expert interpretation. For some methods the use of bifrontal electrodes has been developed. Interpretation of the electrical signals with Fourier analysis describes the component waveform frequencies and amplitudes which can be displayed in a number of ways, for example as the compressed spectral array. As anaesthesia deepens the amplitude of the high frequency components falls with an increase at the lower frequencies. These changes are agent dependent, limiting the use of this technique as a depth of anaesthesia monitor. The Patient State Index is one EEG method of assessing hypnosis and was developed by comparing large numbers of EEGs during induction, maintenance and emergence. It assesses the patient EEG (mainly in the antero-posterior direction with less electrodes than conventional raw EEG acquisition) and calculates an index of hypnosis.[7] It is currently under clinical validation.

The Bispectral Index monitor (BIS) quantifies the phase relationships among the underlying sine wave components of the EEG and with the power and frequency information calculates a single numerical variable. 100 corresponds to the awake EEG and 0 to electrical silence. In applying it clinically a value of 65 to 85 is recommended for sedation and 40 to 65 as general anaesthesia. It has been found to correspond linearly with the hypnotic dose of intravenous or volatile agents used, correlating well with the hypnotic state and importantly is agent independent. However in comparison with MAC, BIS poorly predicts a movement or non-movement response, especially in the presence of opiates.[8]

BIS seems attractive as a monitor for intravenous as well as conventional volatile anaesthesia, but does it reduce awareness? Explicit awareness is uncommon so for a trial to have adequate power to show a significant reduction it would need to be very large.[2] Despite one recent trial[9] in nearly 5000 patients showing a reduction in explicit awareness compared to the incidence in a historical control group, there is limited clinical evidence to support this finding thus far.[2] Hypnotic titration, where the

intravenous or volatile agent is titrated to a target BIS value, has been studied. Its use has shown a reduction in anaesthetic usage with faster emergence times however no difference in the time for hospital discharge.[2,10] BIS does not actually correlate as well with measured propofol concentration as with an observer assessment of awareness and one concern is that in encouraging anaesthetists to run lower concentrations of anaesthetic agent to maintain a target BIS value it may encourage higher risk anaesthesia, potentially increasing the risk of awareness.

Some practical problems related to EEG based monitoring may occur. The EEG signal is prone to electrical interference in the theatre environment, especially with the use of diathermy and EMG activity from facial muscle and high electrode impedances may falsely elevate the calculated BIS values. The BIS cannot be used with ketamine due to its properties of EEG excitability and inaccuracies may arise with the use of nitrous oxide, which causes no change in BIS up to a concentration of 50%.

Auditory evoked responses (AER) represent the passage of electrical activity from the cochlea to the cortex in response to auditory stimuli administered via headphones, usually at 6-10Hz. These consist of an early brainstem response followed by early and late cortical responses. EEG analysis of the early cortical, (middle latency), activity reveals characteristic waveforms whose latency increases and amplitude decreases with the onset of anaesthesia, with subsequent reductions in amplitude as anaesthesia deepens.[11] AER monitoring correlates well with the transition from the awake to the asleep state, however predicts movement in response to painful stimuli poorly.[12] A middle latency AER monitor has been developed which calculates an index, (AAI) of 100 to 0, however it has not yet gained wide popularity as a depth of anaesthesia monitor. This may be partly due to problems relating to signal interference but also when comparing it to bispectral index the AAI monitor shows wide variation in awake values and overlap between the awake and asleep state. It has been reported to have successfully detected awareness intraoperatively[3] however and may emerge as a useful tool in the future.

Bispectral Index Values	
100	awake
65 - 85	sedation
45 - 65	general anaesthesia
<40	burst suppression
0	no electrical activity

MAC

The measurement of end-tidal volatile anaesthetic agent concentration is a standard component of modern anaesthetic monitoring. It led to the concept of MAC and provides the best available method to monitor continuous brain concentration of volatile anaesthetics provided adequate time is allowed for equilibration between alveolus, blood and effect site. Inhalational agents including nitrous oxide are considered additive in their actions and contribution to MAC but it must not be forgotten that their pharmacokinetics are different depending on relative solubilities.

MAC is the minimum alveolar concentration of anaesthetic agent at 1 atmosphere pressure producing immobility in 50% of subjects exposed to a standard painful stimulus and has been studied extensively in animals and humans. Two common designs are used, quantal and bracketing.[13] Quantal study designs, used in human trials, involve the exposure of a known concentration of agent for a defined time whereupon a standard noxious stimulus is applied. Movement or non-movement is recorded. The probability of non-movement as a function of anaesthetic dose can be calculated for the population with MAC being the 50% effective dose (ED50). MAC is normally distributed. Bracketing designs calculate MAC for individual animals by incremental changes in dose until non-movement to pain occurs. The two methods correlate closely. Due to the accuracy of modern gas analysers and the move/non-move endpoint MAC studies are precise, showing a low biological variability in MAC with standard deviations quoted at 10-20%.[14]

The movement response to a skin incision under volatile anaesthesia is mediated partly at a spinal level by inhibiting spinal reflexes 8. This characteristic of inhalational anaesthetics is not shared by the intravenous anaesthetic propofol. The observation that patients lose consciousness at anaesthetic doses less than 1MAC led to the concept of MACawake This is more difficult to determine accurately, varying between agents, but is around 0.5MAC or less for the less soluble agents. MACawake being less than 1 MAC is reassuring in terms of awareness during anaesthesia.

MAC is decreased by a number of factors. These include decreasing body temperature, hypoxia and acidosis, sedative drugs including alpha2 agonists, systemic and epidural opiates and also with age. This reduction with age occurs at the same rate for all volatile agents and was quantified and published by Mapleson who calculated a 6% decline per decade after the first year of life. The concept of age-related MAC has been developed with the publication of age-related iso-MAC charts[15] and more recently an age-related MAC nomogram.[16] These charts allow the estimation of appropriate end-tidal isoflurane, sevoflurane and desflurane concentration to provide particular MAC values over a range of ages and in the presence of 0%, 50% and 67%

Variants of MAC	
MAC	The minimum alveolar concentration of anaesthetic at 1 atmopshere pressure producing immobility in 50% of subjects
MAC_{awake}	The minimum alveolar concentration of anaesthetic producing unconsciousness in 50% of subjects
MAC_{bar}	The minimum alveolar concentration of anaesthetic producing blocking the sympathetic nervous system response to a painful stimulus in 50% of subjects

EEG-based Methods of Monitoring Depth of Anaesthesia	
Raw EEG Multiple leads	19 Lead Bulky Difficult Interpretation Inter-anaesthetic agent differences
Compressed Spectral Array Frontal electrodes	Graphical display of component EEG frequency amplitudes Fourier Analysis Reduced higher frequency, increased low frequency amplitudes with anaesthesia Easier to interpret than raw EEG Agent dependent changes
Patient State Index	Index of state of hypnosis/awareness From retrospective analysis of multiple 19 lead EEGs throughout anaesthesia Compares EEG to population electrophysiological distribution of EEG changes Agent independent Predicts anaesthetic state with PSI value
Bispectral Index Frontal electrodes	Combines spectral array and phase relationships of component sine waves Provides single numerical value 0-100 (complex statistical analysis) Correlates linearly with dose of hypnotic agent Agent independent In hypnotic titration BIS reduces anaesthetic dosage and recovery time Does not affect time to discharge Inaccurate with ketamine Not yet established whether BIS reduces incidence of awareness
Auditory evoked potentials Vertex, mastoid, forehead electrodes	EEG activity in response to auditory clicks via headphones Characteristic early cortical responses that change with anaesthesia Reduced latency and amplitude of waveform with anaesthesia Correlates with awake to asleep transition Clinical monitor developed but inter-patient variability in values
General problems	Electrical interference (mains, diathermy, facial muscle EMG) Electrode impedance may cause inaccuracies Excitatory anaesthetic agents cause inaccuracies (ketamine) Patients with abnormal EEG's (Fitting, head injury, etc)

nitrous oxide. They show a wide variation in MAC at extremes of age exaggerated further by the age variation in MAC for nitrous oxide. These are clinically very useful in preventing not only awareness but also the administration of too much anaesthetic to the elderly.

MACbar is the minimum alveolar concentration of anaesthetic agent inhibiting the sympathetic nervous system response to a standard noxious stimulus in 50% of subjects. It shows some variation between agents however is universally reduced by the administration of opiates. Beyond a certain dose no further reduction occurs. Opiates alone do not produce anaesthesia regardless of dose despite producing a small reduction in MACawake therefore it is still essential to administer enough anaesthetic agent to prevent awareness even when high doses or potent opiates like remifentanil are used, for example during cardiac surgery. This is also the case when regional blocks are used to abolish surgical stimulation.

Despite the advances in some EEG-based anaesthesia monitoring, the low inter-patient variability in MAC measurements still suggest that end-tidal agent monitoring provides anaesthetists with the best guide to assessing anaesthetic depth. It is not so easy to simply compare confidence intervals of MAC measurements and EEG derived monitoring for a number of reasons. During the development of BIS monitoring it was tested in the context of volatile anaesthesia and move /non-move endpoints. However with the increasing use of intravenous anaesthesia, the effect of opiates on the move endpoint, its inferior ability to predict movement compared to volatile agent monitoring and the difference in the hypnotic and analgesic components of anaesthesia, the software was reformulated.[8] A recent study assessing BIS values in children receiving various doses of isoflurane showed standard deviations of around 30% around

Factors increasing MAC	**Factors decreasing MAC**
Age: children	Age: elderly
Hyperthermia	Hypothermia
Hyperthyroidism	Hypoxia
Alcoholism	CNS depressants
	N_2O and other volatile agents

the mean BIS values.[17] It has already been mentioned that the inter-patient variability in the pharmacokinetics and pharmacodynamics of propofol during its administration by target-controlled infusion systems is large making its assessment of anaesthetic depth during total intravenous anaesthesia less reliable.

1.0 MAC: **End tidal isoflurane in:**			
Age	**100% O_2**	**50% N_2O**	**67% N_2O**
1	1.5	0.95	0.75
10	1.4	0.85	0.65
20	1.3	0.75	0.55
30	1.25	0.65	0.5
40	1.15	0.6	0.4
50	1.1	0.55	0.35
60	1.05	0.45	0.25
70	1	0.4	0.2
80	0.9	0.35	0.15
90	0.85	0.3	0.1

Lower oesphageal contractility

Spontaneous and provoked lower oesophageal contractions both reduce in latency and amplitude during general anaesthesia. These are measured using a balloon in the oesophagus however published evidence of its use as a depth of anaesthesia monitor is limited.

Conclusion

It seems that the measurement of end-tidal volatile agent concentration currently provides the most objective estimate of brain anaesthetic concentration available and has stood the test of time. Quantifying the effect of anaesthetics on brain activity is an attractive proposition for monitoring both volatile and intravenous anaesthesia and in time EEG-based monitoring may prove to be a sensitive indicator of depth of anaesthesia to use in conjunction with the conventional means at our disposal to prevent intra-operative awareness.

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