CHAPTER
20

Depth of anaesthesia monitoring

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HEADLINE

20.1 Specific depth of anaesthesia (DOA) monitors are rarely used in UK anaesthetic practice: in only 2.8% of general anaesthetics for processed EEG (pEEG) and 0.03% for the isolated forearm technique (IFT). Of the 141 reports to NAP5 judged to be Certain/probable/possible AAGA, six (4.3%) occurred despite use of a pEEG monitor. However lack of detail means appropriate and continuous use cannot be confirmed. These monitors appeared to be used in a 'targeted fashion': for instance, in the Activity Survey, whereas pEEGs were used in only 3.5% of cases where volatile and neuromuscular blockade (NMB) was used, they were used in 23.4% of cases with total intravenous anaesthesia (TIVA) and NMB. A crude analysis of the cases of AAGA in which pEEG was used or omitted was not able to detect whether there was a marked protective effect of its use. Only one report of AAGA in association with DOA monitoring was followed by adverse psychological sequelae. The possibility of a more subtle benefit of DOA monitors in protecting against 'AAGA with sequelae' merits investigation. Although end-tidal anaesthetic gas monitoring is an alternative to DOA monitoring, in ~75% of reports to NAP5 it would probably have been impractical or ineffective at preventing AAGA. The overall findings are supportive of the use of DOA monitoring in selected circumstances, but provide no support in others.

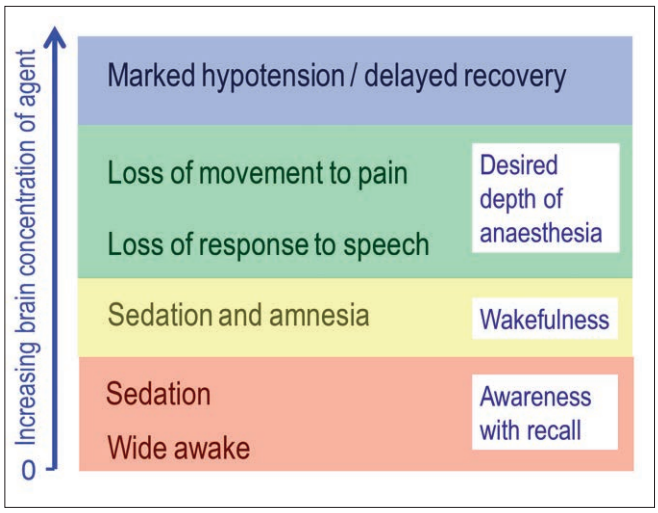
BACKGROUND

20.2 The level of consciousness in another person (a patient) is in large part assessed by the degree to which they respond or not to increasing stimuli. A patient is regarded as fully conscious when they are responsive even to mild verbal interrogation. A lack of response to speech, or immobility as the result of administration of a hypnotic/narcotic drug is taken to represent increasing depths of unconsciousness, and when there is no response even to sustained painful stimulus, the patient is judged to be in a sufficiently 'deep' plane of anaesthesia. At least, this is the case when no neuromuscular blocking drug is given, as then the patient retains the capacity to respond.

20.3 However, when a neuromuscular blocking drug is used, the capacity to respond is lost, regardless of the level of consciousness. As noted elsewhere (Chapter 19, Neuromuscular blockade) the degree of motor capacity can be objectively assessed using a nerve stimulator. In the presence of neuromuscular blockade, it becomes impossible using clinical signs (including autonomic signs) of responsiveness alone to distinguish an awake, paralysed patient from one who is suitably anaesthetised (Schneider & Sebel, 1997).

20.4 A typical pattern of effects resulting from an increasing brain concentration of an anaesthetic drug such as propofol or a volatile anaesthetic agent is broadly illustrated in Figure 20.1.

Figure 20.1. Crude representation of the effects of increasing brain concentrations on anaesthetic responsiveness in an unparalysed patient. Within the white boxes are shown the likely results in a paralysed patient, were surgery to proceed at the given level of consciousness. The brain concentration at which these effects occur varies between individuals



20.5 Certain aspects of drug dosing are well established and involve both pharmocodynamics and pharmacokinetics. Older patients typically require a lower brain concentration of an anaesthetic to produce loss of awareness than do younger patients; body weight or male-female differences can influence volumes of distribution of anaesthetic agents (Buchanan et al., 2011). The co-administration of other drugs with anaesthetic or sedative effects such as nitrous oxide, benzodiazepine or opioids reduces the brain-concentration of anaesthetic required (Aranake et al., 2013). However, there is considerable variation between individuals so that the brain concentration required to produce loss of awareness in an individual cannot be accurately predicted in advance (Aranake et al., 2013).

20.6 While it is possible to ensure unconsciousness and prevent AAGA by administering very large doses of drug, this may increase the incidence of adverse effects including delayed recovery, nausea and vomiting and post-operative confusion, but hypotension (and its sequalae) is arguably the most important.

20.7 Hypotension may add to risks of surgery, especially in those patients with pre-existing co-morbidities. In certain circumstances the incidence of hypotension during anaesthesia is markedly increased e.g. hypovolaemia, cardiac disease and cardiovascular drugs. The anaesthetist may decrease the anaesthetic dose in response to a low blood pressure (or to prevent its occurrence) and there is a risk of inappropriate or excessive reduction leading to awareness. Hence there is a genuine problem of titrating the anaesthetic to the correct dose (Yu & Liu, 2013).

20.8 In other words, the sensitivity of the brain (in terms of the hypnotic/narcotic effects of the drug) is not necessarily identical to the sensitivity of the other body systems, especially cardiovascular (e.g. in terms of the hypotensive effects of the drug).

20.9 There is a further problem, that when a neuromuscular blocking drug is given, the *capacity* to respond by movement is abolished and it becomes impossible to assess if the patient is adequately anaesthetised. Unfortunately indirect autonomic or involuntary responses (such as an increase in heart rate, blood pressure or lacrimation) have all proved unreliable signs of consciousness. They can also be influenced directly by the surgical process, or by other non-anaesthetic drugs i.e. these reflexes can be activated by processes independent of consciousness (Schneider & Sebel, 1997), and there is good evidence from large series that autonomic responses are uncommon in cases of reported AAGA (Domino et al., 1999; Ghoneim et al., 2009).

20.10 The 'anaesthetist's dilemma' of how to detect consciousness in a paralysed patient is addressed in practice by using a dose of hypnotic agent which experience suggests is sufficient to prevent recall in the large majority of patients. An alternative approach is to attempt to assess whether the individual patient is receiving adequate hypnotic drug by using a monitor of depth of anaesthesia (DOA) such as the isolated forearm technique (IFT) or a processed EEG (pEEG) monitor.

20.11 However, unless the monitor is entirely empirical (i.e. based purely on coincidental correlations of monitor output to brain state), the monitor output needs to be both generated and interpreted in the light of some macroscopic model of consciousness. In this way, three fields of enquiry are inter-related: (a) the nature of consciousness (in terms of a philosophical, conceptual understanding and a neuro-anatomico-physiological model), (b) the nature of anaesthesia (in terms of relevant neuroscientific mechanism) and (c) the principles of monitoring (in terms of how to detect a given state). As there is considerable scientific uncertainly regarding the nature of consciousness, this creates a logical problem with development of such monitoring.

20.12 Two approaches to monitoring are IFT and pEEG monitoring.

Isolated forearm technique

20.13 In the IFT, a tourniquet applied to one upper limb is inflated to above the arterial blood pressure before a neuromuscular blocking drug (NMB) is given into a vein elsewhere in the body (Tunstall, 1977; Russell, 2013a and b). Therefore, the NMB does not reach the neuromuscular junctions beyond the tourniquet and movement of the hand on that side remains possible. The anaesthetist can then observe the hand for either reflex movements or responses to command. In effect, the same assessment is now possible as in a patient who has not received an NMB (Table 20.1 and Figure 20.2).

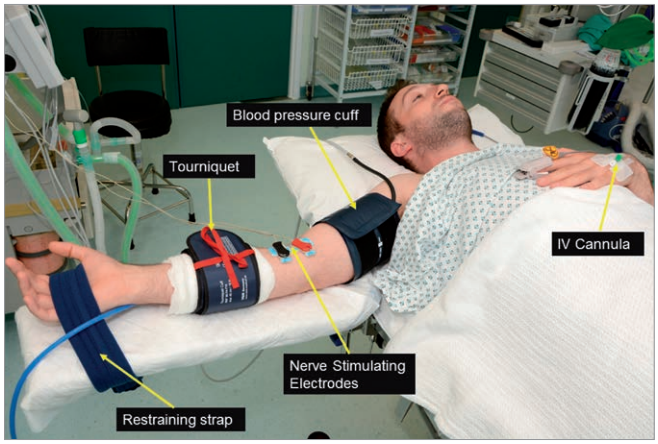
20.14 The IFT construct has, in a very elegant way, conferred or retained motor capacity in an otherwise paralysed patient. A positive motor response to command during IFT is termed 'wakefulness' (Wang, 2012): i.e. the patient is potentially awake and exhibiting signs of this, but may not have any recall of this after surgery.

Table 20.1. Russell's modification of the isolated forearm technique for prolonged use (Russell, 2013)

1.	Insert IV cannula in left forearm
2.	Apply BP cuff to right upper arm
3.	Apply padded tourniquet to right forearm
4.	Apply nerve stimulating electrodes to ulnar and/or median nerves at right elbow
5.	Induce anaesthesia, inflate tourniquet, check neuromuscular integrity, give judicious dose of relaxant and intubate
6.	Provide maintenance anaesthesia
7.	After 20 minutes deflate tourniquet
8.	If more relaxant is required inflate tourniquet give top-up dose of relaxant
9.	After 20 minutes deflate tourniquet
10.	Repeat steps 8 – 9 as required

If there is a hand response then verify this by giving the patient a different command. Neuromuscular integrity should be checked at regular intervals.

Figure 20.2. Russell's modification of the isolated forearm technique



20.15 In a study using the IFT, during most episodes of wakefulness there was no increase in heart rate or blood pressure, and no sweating or tear production suggestive of inadequate anaesthesia (Russell, 1993).

20.16 Remarkably, the reported incidences of a positive response during IFT are very high, with over a third of patients responding (Sanders et al., 2012). This may, at least in part, be because some studies employ very low doses of anaesthetic drugs, considerably lower than is perhaps usual in clinical practice (e.g. Russell, 2013a and b). A study using more conventional doses of anaesthetic drugs found a much lower incidence of responsiveness during IFT (Andrade, 2008) though not all the patients in that study received a neuromuscular blocking drug.

20.17 However, few anaesthetists have adopted the technique. The NAP5 Baseline Survey suggested only 14 of over 8,500 senior staff in the UK ever use IFT (Pandit 2013a and b). This may be because of lack of familiarity, because they perceive it to be a relatively difficult and time consuming technique to use which may distract from other aspects of patient monitoring and care or even because they do not consider it a technique of any value (Sleigh, 2013).

20.18 The state of *wakefulness or awareness without recall* identified by IFT may be the same or a very similar state as that of sedation and amnesia, commonly seen in patients who have not received a NMB and are undergoing a procedure under sedation with or without additional analgesia or regional anaesthesia. On the other hand, Pandit (2013 & 2014) has argued that when IFT patients respond to command but do not move the arm spontaneously during surgery, this represents a unique brain state (dysanaesthesia) in which the patient's perception is partially uncoupled from

sensation: that is, fully uncoupled in respect of surgery but remains coupled to verbal stimulus (Pandit, 2014). This, Pandit predicts, will (if anything is recalled) give rise to a largely neutral memory of surgery. This theory does not question the IFT as a suitable technique, but offers different interpretations of this 'monitor output'.

20.19 Recall of wakefulness after use of an IFT technique – i.e. explicit awareness – is rare. Of note there are no large studies that indicate a reduction in reports of AAGA by use of IFT. During the IFT some patients have indicated discomfort but it is not known through large cohorts whether there are long term psychological effects of this, or of being aware but comfortable.

20.20 The correlation (or lack of it) of IFT results and pEEG monitoring is discussed below.

Processed EEG monitoring

20.21 Electronic DOA monitors use forehead surface electrodes to measure the EEG, which is then processed. The most commonly used general anaesthetic drugs – propofol, thiopental and the volatile anaesthetic agents all – produce a similar pattern of EEG changes with increasing brain concentrations, and the corresponding increasing 'depth' of sedation and anaesthesia.

20.22 With increasing depth of anaesthesia, the relevant EEG changes include – in order – an initial increase in high frequency components, then an increased proportion of low frequency EEG components, an increase in amplitude of the EEG waveform, increased regularity of EEG signal (i.e. decreased entropy), burst suppression (i.e. periods of an isoelectric EEG) with deep anaesthesia and a completely isoelectric 'flat line' EEG with very deep anaesthesia.

20.23 In addition to displaying the EEG waveform, DOA monitors derive a number or index which is intended to indicate the degree to which the electrical activity of the brain is affected by an anaesthetic drug. For example, the BIS monitor displays an index between 0 and 100. This is generated by use of an algorithm based on specific measures in the pEEG but the details of this algorithm are a commercial secret. At BIS values of 60–80, the subject may respond to mild prodding or shaking, whereas values of 45–60 are associated with a 'low probability' (unquantified) of explicit recall. A BIS level of <45 is a 'deep hypnotic state' (see: www.covidien.com).

20.24 Ketamine, nitrous oxide and xenon do not produce the same pattern of EEG changes as described above. The use of the indices from pEEG monitors to guide anaesthetic administration is therefore less useful if these are amongst the anaesthetic drugs being used (Lobo & Schraag, 2011). It is not fully established how pEEG monitors perform when these drugs are used to supplement anaesthesia maintained with a volatile agent or propofol.

20.25 Even those anaesthetic drugs that lead to EEG changes reflected in changes in BIS index do not affect it identically. Therefore the probability of awareness with a given BIS score varies between agents – though the differences are modest (Glass et al., 1997; Ibrahim et al., 2001; Schwab et al., 2004).

20.26 Other than the BIS, pEEG-based depth of anaesthesia monitors used in the UK include the Narcotrend monitor and the E-Entropy monitor. DOA monitors which analyse the EEG response to auditory stimuli, i.e. auditory evoked potentials are also available but are less commonly used in the UK (Pandit et al., 2013a and b).

20.27 Several large, randomised studies have either compared anaesthesia guided by a pEEG monitor with 'standard care', or with a protocol designed to maintain a specified minimum end tidal anaesthetic gas (ETAG) concentration.

20.28 The B-Aware trial (Myles et al., 2004) compared BIS-guided anaesthesia with standard care in 2,463 adult patients (with neuromuscular blockade) at increased risk of awareness. The result was in favour of BIS, with two reports of AAGA in the BIS-guided group and 11 reports in the routine care group ($p=0.022$).

20.29 In contrast, the B-Unaware (Avidan et al., 2008) and BAG-RECALL (Avidan et al., 2011) studies compared BIS-guided anaesthesia with a protocol in which alarms were used to prompt the anaesthetist to keep the ETAG >0.7 MAC (age-adjusted). These found BIS to make no difference to the incidence of AAGA.

20.30 A Cochrane review (Punjasawadwong et al., 2007; updated in 2010) concluded that BIS-guided anaesthesia could reduce the risk of intra-operative recall in surgical patients who had a 'high risk' of awareness, when otherwise clinical signs were relied upon, but not if a protocol using ETAG alarms was used.

20.31 Based in part on this and its own analysis, NICE produced a Diagnostics Guidance report (2012) which recommended that pEEG monitoring is an 'option' in patients considered at 'higher risk' of AAGA and patients at higher risk from excessively deep anaesthesia. Furthermore, NICE stated that pEEG monitors are recommended as an option in

all patients receiving total intravenous anaesthesia (TIVA).

20.32 However, the NICE recommendations were questioned by Pandit & Cook (2013), who amongst other criticisms, noted that the terminology surrounding this advice remained unhelpfully vague. Thus the Cochrane review, perhaps unusually imprecisely, suggested pEEG monitors 'could' (rather than 'did') achieve the intended aim, and NICE only recommended it as an 'option', in a *higher risk* (undefined) category of patients. As a relatively new technology, no algorithms as to how to respond to, or interpret the monitor outputs were referred to. Perhaps the vague terminology is an accurate reflection of the pressing need for further research. The NICE report applied these recommendations to BIS, Narcotrend and Entropy equally, despite acknowledging the markedly less robust data supporting this view for the last two devices.

20.33 Furthermore, the relationships between a given pEEG monitor output (e.g. BIS reading of, say, 45 vs 55 vs 65) and the probability of consciousness is not fully ascertained.

20.34 A BIS value of <60 is said to be associated with a low probability of explicit recall but Russell (2013a and b) and Zand et al. (2014) have demonstrated that this does not necessarily mean a low probability of wakefulness without recall when using the IFT.

20.35 In addition to their use in guiding the appropriate depth of anaesthesia to prevent AAGA, DOA monitors have also been advocated as a means of avoiding excessively deep anaesthesia. This is associated with hypotension, delayed recovery and possibly increased mortality and mortality. The combination of a low BIS, low BP and low MAC values (defined as >1 standard deviation below the mean) appears to be associated with an increased 30 day mortality and increased length of hospital stay (Sessler et al., 2012). A randomised trial, the Balanced Anaesthesia Study, is being undertaken in which one year mortality rates will be compared in patients randomised to BIS targets of either 50 or 35 (see: http://balancedstudy.org.nz/).

End-tidal monitoring

20.36 ETAG monitoring with audible alarms appropriately set and turned on is a reliable way of ensuring a given amount of volatile anaesthetic is in equilibrium with body (brain) tissues.

20.37 End-tidal anaesthetic gas monitoring is not, of course, suitable or relevant when an intravenous infusion is used to maintain anaesthesia (TIVA). TIVA can be administered using target-controlled infusion (TCI) pumps which display the estimated plasma and effect-site anaesthetic drug concentrations. However, when TIVA is employed with an NMB, not only is there a limitation on measurement of the conscious level (as with all anaesthetics) but additionally there is no direct measure of the amount of drug within or equilibrated with the body (brain) tissues.

Summary

20.38 In summary whereas in the unparalysed patient, a lack of motor response to stimulus can reasonably be assumed to indicate adequate anaesthesia, this is not the case when neuromuscular blockade is used. However, all measures have their limitations. The IFT cannot be used in all cases the output of pEEG monitors does not relate to specific brain functions, and ETAG monitoring measures drug concentration rather than brain responses. TIVA poses special challenges to ensuring the correct dose is delivered. It might therefore be predicted that AAGA might be higher when neuromuscular blockade is used, or when TIVA is employed. If pEEG monitors are effective, then we might expect to see fewer patients in whom they had been used reporting AAGA than in the general surgical population. However such a reduction might not be apparent if pEEG monitors are more frequently used in patients at high risk of AAGA than in patients at low risk.

NAP5 CASE REVIEW AND NUMERICAL ANALYSIS

20.39 Of the 141 Certain/probable and possible cases of AAGA, a DOA monitor (always the BIS) was used in six 4.3%, five in Class A and one in Class B. It was not used in any cases arising from ICU or syringe swap/drug errors.

20.40 In the Activity Survey, IFT was used in just five patients during the survey (~0.03% of all general anaesthetics), once when no NMB was used. No reports of AAGA described use of IFT monitoring, but 11 patients moved despite neuromuscular blockade (thus exhibiting a degree of motor capacity which they exercised). This could be regarded as 'IFT by default'.

20.41 Overall, pEEG monitoring was used in 2.8% of all general anaesthetics in the Activity Survey. This superficially implies an over-representation of the use of pEEG monitoring in the AAGA cases (by a factor of ~1.5; Table 20.2).

20.42 However, more detailed consideration is warranted, especially concerning the use of TIVA and neuromuscular blockade.

20.43 Table 20.2 shows how the combinations of volatile, TIVA and neuromuscular blockade were used in the Activity Survey. The data show a preponderance of volatile over TIVA for maintenance anaesthesia. In slightly over half of the volatile anaesthetics no NMB was given; however, when TIVA was used, it was slightly more common for NMBs to be given.

20.44 The data in Table 20.2 represent a crude 'AAGA risk profile' of the given technique. The most common technique was a volatile without paralysis and this was under-represented (ten-fold) in the cases of AAGA. However, any technique employing paralysis was over-represented, especially TIVA with neuromuscular blockade, which was more than three times as frequently seen in AAGA cases as it was used generally.

20.45 These data are not amenable to any meaningful statistical comparisons as the numbers in some categories are very small; hence this is classed as a crude risk profile that might help focus further research.

20.46 An important caveat to this crude data is that several of the TIVA cases in which AAGA was reported used a non-TCI TIVA technique and/or took place outside the operating theatre in situations where the administration of a volatile anaesthetic was not possible. Thus a more nuanced analysis is appropriate – see Chapter 18 TIVA.

20.47 It could be argued that the ten failed intubations (none of which included TIVA) were all part of an intended volatile technique. While this changes the detail of the ratios in Table 20.2 somewhat (volatile without NMB 0.11, volatile with NMB 2.1, TIVA without NMB 0.63 and TIVA with NMB 3.2) the message remains the same.

20.48 Table 20.3 shows the use of pEEG monitoring across the types of anaesthetic techniques employed. It indicates that anaesthetists use pEEGs apparently highly selectively: uncommonly when volatiles are used (and hardly at all when volatiles are used without NMB), but more commonly during TIVA (and especially when TIVA is used with NMB).

20.49 The ratios of pEEG use offer the opportunity to attempt to calculate a very crude 'protection profile' of pEEG monitoring use.

20.50 By comparison with Table 20.2, and notwithstanding the small numbers involved for some types of anaesthesia, pEEG monitoring appears to confer no advantage when no NMBs are used.

20.51 Again, this data is not amenable to any meaningful statistical analysis due to the low numbers in some cells (and in the case of volatile with no NMB technique, a zero numerator). Thus the data do not persuasively indicate whether pEEGs are protective or not. However, TIVA used with NMB yields the lowest ratio, suggesting that the greatest potential benefit of pEEG monitoring (if one exists) is most likely to be demonstrated with this technique.

Table 20.2. 'Risk profile' of different anaesthetic techniques for AAGA. Proportions of anaesthetic technique as used in the Activity Survey (n rounded up to nearest 100), compared with their representation in cohort of AAGA cases. Of the 141 Certain/probable and Possible cases, 23 were excluded as: failed intubations (judged neither volatile or TIVA, but appeared intended volatile), mixed methods (using both volatile and IV anaesthesia, either concurrently or sequentially and indeterminate techniques. This left 118 as the denominator for this second column). In the last column, a ratio of >1 indicates over-representation in the AAGA cohort; <1 indicates under-representation. The greatest over-representation in AAGA cases if for those techniques using NMB, especially with TIVA

	Activity Survey GAs with NMB specified n = 2,667,000 (%)	Proportion of AAGA cases with NMB specified n = 118 (%)	Ratio of AAGA % to Activity Survey %
Volatile, no NMB	50.9% (n= 1,357,600)	5.9% (n=7)	0.12
Volatile, NMB	41.1% (n=1,095,100)	76.3% (n=90)	1.86
TIVA, no NMB	3.7% (n=95,200	2.5% (n=3)	0.68
TIVA, NMB	4.1% (n=108,400)	15.3% (n=18)	3.73

20.52 A limitation of the analysis above is that it assumes first, that there is no systematic selection of anaesthetic technique according to other putative risk factors for AAGA, and secondly, that use of pEEG is not selective beyond type of anaesthetic. If, for instance, in patients who are suspected to be more likely to have AAGA (e.g. patients who are younger, female, obese, having higher risk surgery or with other risk factors for AAGA), there is unequal distribution of anaesthetic techniques used or of use of pEEG, then this could impact the conclusions that can be drawn from both Tables 20.2 and 20.3. Thus our conclusions should be judged with this caveat.

20.53 Of the five Certain/probable AAGA cases that employed a BIS monitor, only one experienced distress (as a result of paralysis). One patient experienced each of paralysis without distress, auditory sensations, touch, and paralysis with pain (but no distress). There was no longer-term impact as judged by modified NPSA scores, except in the patient experiencing touch, whose case the score was judged Moderate. The patient in the Possible category whom a BIS monitor was used had complained primarily about poor post-operative pain relief. They had also said that they were 'unhappy at waking up during the operation' but gave no details of the possible awareness experience. Thus, the cohort of patients who experienced AAGA when a BIS was employed, in the main experienced very modest impact and in general without distress related to the experience.

Nine months after abdominal surgery, an elderly patient mentioned overhearing a few seconds of conversation between surgeons during his operation regarding the position of the incision and other operative details, and quoted exactly what had been discussed. After intravenous induction including neuromuscular blockade, maintenance used a volatile agent (MAC charted as 0.9 at time of AAGA) and BIS was used and was charted as being in the 40s throughout. The patient was not concerned by the experience; but rather interested by it.

A middle-aged patient underwent a general surgical procedure and immediately after reported "I knew I was in trouble and I wanted to tell you but I couldn't move". The patient had no recollection of the event the next day when questioned specifically about it by the anaesthetist, and was dismissive of it all saying "It must have been just me". Anaesthesia was induced and maintained with propofol and remifentanil infusions and an NMB. BIS monitoring was used. An NMB was given not long before the end of surgery, resulting in a period of about 15 minutes after the completion of surgery before the muscle relaxation could be safely reversed. The impression was that the episode of awareness probably occurred after the end of surgery and before full recovery from the NMB. BIS was <35 during the procedure and <45 at the end of the procedure.

Table 20.3. Estimating 'protective effect' of pEEG monitoring. Proportions of pEEG monitoring use in general anaesthesia types in the Activity Survey and in the Certain/probable and Possible AAGA cases where pEEG monitoring used. In the last column, a ratio of <1 indicates use of the monitor may have a 'protective' effect against AAGA, such that there is under-representation in the AAGA cohort; >1 indicates the reverse. Monitoring appears to exhibit the greatest reduction of risk for TIVA with NMB

n in Activity Survey	pEEG monitoring (n) as % of totals in Activity Survey	pEEG monitoring (n) as % of AAGA cases	Ratio of pEEG use in AAGA %: Activity Survey % (expected n from Activity Survey)
All GAs with use or omission of NMB specified (n= 2,667,600)	2.8% (n=73,600)	5.1% (n=6)	1.82
Volatile, no NMB (n=1,357,600)	1.1% (n=15,000)	0.0% (n=0)	zero numerator
Volatile, NMB (n=1,095,100)	3.5% (n=38,300)	3.3% (n=3)	0.94
TIVA, no NMB (n=95,200)	7.8% (n=7,400)	33.3% (n=1)	4.27
TIVA, NMB (n=108,400)	23.4% (n=25,400)	11.1% (n=2)	0.47

20.54 Particular caution needs to be exercised if the index value from a pEEG monitor suggests that the patient is adequately anaesthetised, but either the dose of anaesthetic being administered is unexpectedly low for that patient, or there are clinical signs that might suggest inadequate anaesthesia.

An elderly patient underwent urgent surgery for bleeding after cardiac surgery. During positioning for surgery increased blood pressure and heart rate were noted by the anaesthetist and additional anaesthetic agents administered. When the anaesthetist reviewed the patient the next day, the patient recalled waking up whilst being positioned and accurately hearing discussion but being unable to communicate. There was some distress and the patient was concerned about possible awareness during any further general anaesthetics. A volatile anaesthetic followed an intravenous induction with neuromuscular blockade with ETAG levels held intentionally between ~0.4- 0.6 MAC and a BIS used to titrate this, with all charted values <60.

An elderly patient reported AAGA after an abdominal operation. The patient reported that they could hear people talking, that they were aware that their abdomen was being closed and that they had a tube in their mouth; then they went back to sleep. The patient experienced some pain but seemed unconcerned by the episode. An intravenous induction was followed by volatile anaesthesia maintenance with neuromuscular blockade. The end-tidal sevoflurane was charted as low as 0.4 MAC, a remifentanil infusion was used and the BIS was charted during surgery as <55.

20.55 Caution also needs to be exercised if, in fact, the BIS readings exceed the recommended upper limit of 60. If a patient later makes a report of AAGA (even one that is vague in detail), then it would be consistent with the published guidance to interpret this as supportive of the patient's report. However the current understanding of BIS monitoring is such that it is not clear how much higher than 60 and for how long a BIS score is needed to make explicit recall likely.

A middle aged patient with a chronic neurological disease and chronic pain underwent orthopaedic surgery and made a very vague report of having been 'aware', that was coupled with other unrelated complaints. A TIVA anaesthetic technique was used, with no neuromuscular blockade and a BIS was used which gave a reading of 65 briefly after the incision but was otherwise <45 (with stable cardiovascular readings).

20.56 Avidan et al. 2008 & 2011 have suggested that a protocol in which ETAG alarms are turned on and set to 0.7 age-adjusted MAC is associated with a low incidence of AAGA. It is not known whether ETAG alarms were turned on in the cases reported to NAP5. However in 80 (72%) of 110 certain/probable reports of AAGA and 106 (78%) of 136 reports that included these and also ICU and drug error cases, the ETAG alarm protocol would have been unlikely to have prevented AAGA. In 22 of these cases anaesthesia was being maintained with intravenous anaesthesia; in 43 cases awareness occurred during or immediately after induction with a bolus of intravenous anaesthetic; in 21 cases awareness occurred at the end of or after surgery after the anaesthetist had turned off the volatile anaesthetic; in two cases it was considered that awareness occurred despite an ETAG concentration of >0.7 MAC; in two cases the anaesthetist deliberately chose to aim for an ETAG concentration of <0.7 MAC (albeit in one case BIS-guided); and in 16 cases awareness occurred as a result of a drug administration error in which an NMB was given before induction of anaesthesia. While ETAG would not have been appropriate in many of these cases, the majority of cases of AAGA reports arise when ETAG would be inappropriate or ineffective.

20.57 In the other 30 cases (22%), an ETAG alarm protocol might have prevented AAGA. However in seven of these cases AAGA occurred in the anaesthetic room or during transfer to theatre, so it would have been necessary for the ETAG alarm protocol to have been used in the anaesthetic room. In a further seven cases the anaesthetist forgot to turn on the vaporiser immediately after transferring the patient into theatre or after inducing anaesthesia in theatre. In this situation an ETAG alarm protocol would only be likely to prevent awareness if the alarm was enabled by default. Otherwise there is a risk that an anaesthetist who forgets to turn on the vaporiser also will forget to turn on the ETAG alarm.

20.58 It is not possible to estimate the extent to which a pEEG monitor might have prevented AAGA in the reported cases. A pEEG monitor could not be expected to have prevented awareness in the 16 cases resulting from drug administration errors (Chapter 13, Drug Errors). In order to have potentially prevented AAGA occurring during or shortly after induction, it would have been necessary (and logical) to have started using the monitor before induction. Similarly, in order to have potentially prevented AAGA cases at emergence,

it would have been necessary to continue using the monitor until recovery from neuromuscular blockade was assured.

DISCUSSION

20.59 One difficulty in interpreting the reports to NAP5 of AAGA in which BIS monitoring was used is that we do not have a continuous record of the output of the BIS monitor, but rather a report of the BIS output at intervals on the anaesthetic record. Thus, we cannot be certain what the BIS values were at the times when the patients had recall of events. It is also not clear whether the monitors were continuously observed, appropriately alarmed or the alarms acted on. Nevertheless, these are cases during which the anaesthetist is likely to have used the DOA monitor as an aid to adjusting the dose of anaesthetic and to have aimed to achieve a BIS value below 60.

20.60 In one of the five Certain/probable AAGA cases, the events recalled by the patient occurred on induction, and it was thought that the BIS monitor may not have been used at that stage of the anaesthetic. In another of the cases the recollection was probably of events after surgery but before full reversal of the NMB, and we cannot be certain whether or not the anaesthetist continued to use the BIS monitor and if so whether they aimed to achieve a BIS value <60 throughout that period.

20.61 In the other three cases, the patients recalled events during maintenance of anaesthesia – one during positioning for surgery, the second during surgical incision and the third during wound closure. These are all periods increased in stimulation and this may have contributed to AAGA at these times. Moving a patient who has a tracheal tube, making or starting to close an abdominal incision are all events that are likely to lead to an increase in 'arousal' and may result in an increase in heart rate, blood pressure and BIS value. The BIS value, like the heart rate and BP, will rise only after the stimulating event.

The displayed BIS value is calculated from data gathered over the last 15 to 30 seconds of EEG recording and updated every second. In a study during which the signal given to a BIS monitor was switched between EEG recordings from awake patients and EEG recordings from anaesthetised patients (Zanner, 2009) it took a mean of 25 s for the value displayed by the monitor to fully reach a value corresponding to the new state.

20.62 In clinical practice if a BIS monitor is used 'reactively' (i.e. the anaesthetist only increases anaesthetic depth when BIS rises above the target range in response to a stimulating event) during light anaesthesia there will be a delay in achieving deeper anaesthesia first for the time for anaesthetist to react and then for the increased anaesthetic drug to have effect. Good anaesthetic practice involves anticipating that an event such as the start of surgery is about to occur and that an increase in anaesthetic drug dose is likely to be required. The DOA monitor may then be used to guide further adjustments after the stimulating event has occurred. Therefore, one criticism of pEEG monitors is that they only provide information about the conscious state after it has arisen. Thus it may be argued, that pEEG monitors sometimes only mitigate the extent of AAGA rather than actually prevent it. What is really needed is a monitor that alerts to a 'pre-conscious' state. However the same argument applies to other modes of monitoring, including the IFT.

20.63 BIS may rise at times of increased surgical stimulus or perhaps simply as a result of fluctuations in brain activity when the surgical stimulus is stable. Maintaining the patient to a target value BIS of 55–60 which (albeit below the upper limits of current guidance) will nevertheless logically expose the patient to greater risk (or probability) of inadequate anaesthesia than if maintained at a BIS 40–50. This underlines the inherent problem of simply using 'threshold values' for pEEG outputs, when in fact the true situation is a highly dynamic one. Anaesthetists should be attentive to all such limitations of DOA (mis)use.

20.64 When DOA monitors are used in patients who have not received an NMB, or in whom the effect of the NMB is wearing off, then forehead and facial muscle electrical activity (electromyography, EMG) may be analysed by the monitor as well as EEG activity. EMG activity is predominantly of higher frequency than EEG activity but there is an overlap in the frequency ranges and the amplitude of the EMG is much larger than that of the EEG. EMG 'contamination' of the EEG signal may result in an increase in the value displayed by the DOA monitor making interpretation of the output more difficult. The Entropy monitor displays two numbers, State Entropy and Response Entropy, with higher frequency EMG activity being deliberately included when the Response Entropy value is derived.

20.65 In a patient whose muscles are not fully paralysed by an NMB, reflex movements in response to painful stimuli may occur despite a DOA monitor

displaying an index value associated with a low likelihood of recall. This situation resembles an IFT-by-default, but it is not known if in this scenario more weight should be given to the patient movement or to the DOA monitor output.

20.66 The reports of AAGA received by NAP5 indicate that the problem of unintended awareness is overwhelmingly that of awareness during neuromuscular blockade (see Chapter 19 Neuromuscular Blockade). In patients who have not received an NMB, clinical assessment of the response to speech and pain is possible and the risk of unintended awareness is low. NAP5 has shown no compelling evidence that DOA monitoring would reduce this further but is not designed so to do (Tables 20.2 and 20.3).

20.67 The clinical trials by Avidan et al (2008 & 2011) suggest that ETAG alarm protocols are as effective as a BIS-guided protocol in reducing the risk of awareness. However, in the B-Unaware study all four cases of definite awareness occurred during surgery and in the BAG-RECALL study all nine of the cases of definite awareness occurred during surgery. In contrast, in the majority of the reports received by NAP5, awareness occurred around the time of induction with an intravenous anaesthetic bolus or at /after the end of surgery when anaesthetic administration had been deliberately reduced or stopped. Therefore, the NAP5 results were generally sparse in relation to the phase of anaesthesia where ETAG monitoring might have the most impact.

20.68 In certain circumstances, DOA values may not be an accurate reflection of the hypnotic state – for example values may be altered by electrical interference, EMG activity or abnormal EEG activity. Some anaesthetic drugs such as nitrous oxide and ketamine do not have the same effects on the EEG as the commonly used intravenous and volatile anaesthetics. NAP5 data do not have the resolution to provide further comment on these aspects.

20.69 Most DOA monitors provide much more information to the anaesthetist than just the derived index value. For example, the BIS monitor (Figure 20.3) provides the EEG waveform, a measure of EEG signal quality, a measure of EMG activity and the Suppression Ratio (i.e. the percentage of the time during which the EEG is isoelectric if burst suppression is present). Optimal use of a DOA monitor involves using all the information it provides together with the information from the other patient monitors, clinical judgement and experience. The DOA value may be a useful extra piece of information but it should be taken along with all the other available information before making a judgement about whether anaesthetic dose should be adjusted.

20.70 However, at present the method of integration of this information remains highly subjective, almost in the manner of an intangible art form. It is desirable to define more precisely exactly how all this information should be optimally or quantitatively combined, and such practical guidance as to *how to* use pEEG monitors (as a question apart from whether to use them) is lacking. Recently, Schneider et al. (2014) proposed a scheme for achieving this, integrating information from BIS and cardiovascular variables to produce a quantitative multimodal index (Sleigh, 2014).

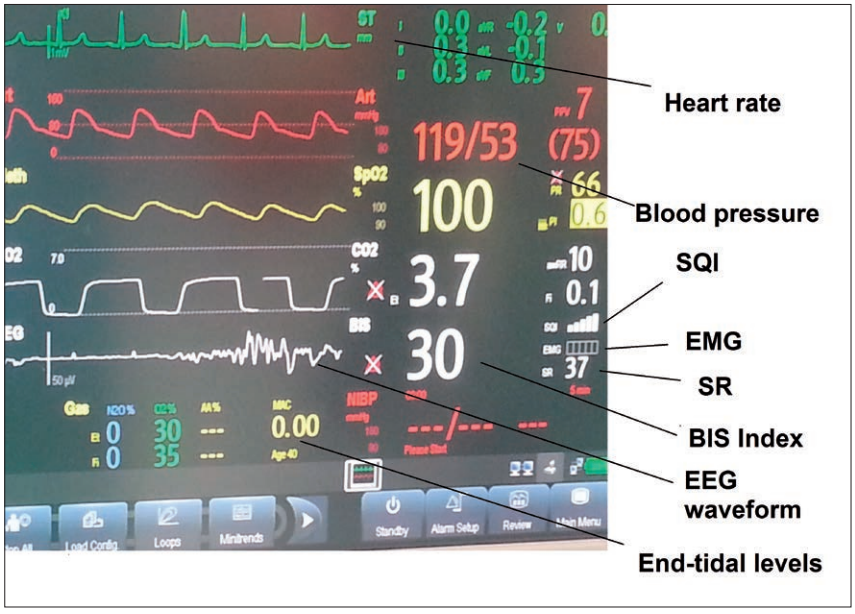


Figure 20.3. An example of the useful additional information available apart from the single numerical output from an EEG-based DOA monitor. The EEG waveform from (in this example) a BIS monitor provides additional information to the BIS index value of 30. Here the EEG shows 'burst suppression' with isoelectric periods indicating deep anaesthesia. The suppression ratio (SR) is the percentage of the time that the EEG is isolectric (37% in this case). There is a high EEG signal quality index (SQI) and no EMG activity has been detected (EMG). The heart rate, blood pressure and end-tidal levels (in this case no volatile or nitrous oxide used), or the estimated plasma or effect site concentration from the TIVA/TCI pump (not shown) also provide additional information. It is desirable to integrate these sources of information to guide the next steps in anaesthetic dosing as suggested by Schneider et al. (2014) and Sleigh (2014).

20.71 These putative objective algorithms would need to address problems such as dichotomy of the information provided by DOA monitor outputs and other variables such as blood pressure or ETAG. For example, when ETAG is very low, it is expected that the pEEG output is high: but what is the best reaction to a situation when it is also low? Problems are also raised by AAGA in the dynamic phases of anaesthesia, induction and emergence, and NAP5 has shown the importance of these phases as times for AAGA.

20.72 It makes theoretical sense to apply DOA monitoring at or before induction if it is planned to use it. However, an ideal monitor would not be contaminated by things like fasciculations or movement of the head and neck that can accompany airway management at induction. How best to react to a situation where the DOA monitor output rises sharply in the middle of airway manipulation or laryngoscopy would need to be defined, especially in the context of a rapid sequence induction or urgent need to secure the airway.

20.73 Zand et al. (2014) reported that during anaesthetic induction for Caesearan section in which IFT was employed, up to 46% of patients moved their hand, but BIS could not discriminate between those who responded and those who did not (no patient had explicit recall). While it may be logical, if using DOA monitors, to apply them from before the start of surgery, further research is needed to interpret their outputs in this dynamic phase of anaesthesia.

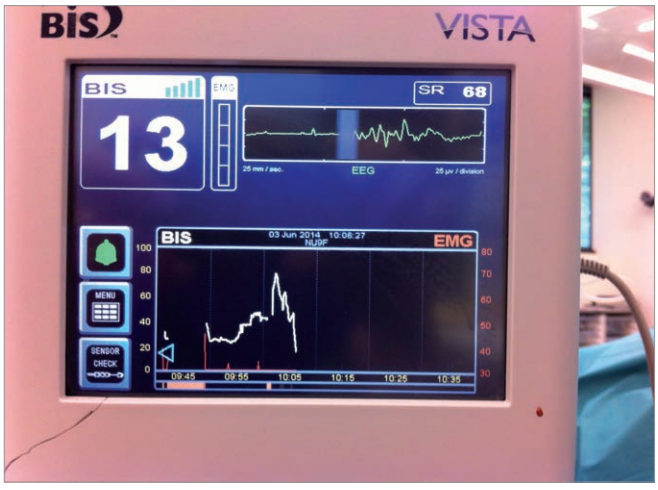
20.74 Similarly at emergence, it is the intention to awaken the patient and DOA monitor outputs are expected to rise; again an ideal monitor would not be contaminated by interference from muscle activity that accompanies this. Perhaps the real utility of DOA monitoring in this phase is to ensure that full muscle power (i.e. motor capacity, as measured by a nerve stimulator) has returned before awakening (as measured by the DOA monitor).

20.75 Although independent evidence for focussing the use of DOA monitoring in patients receiving TIVA is sparse, it is entirely logical when NMB is also used. There are few, if any, ways of monitoring the effect of TIVA in a paralysed patient and point of care blood propofol measurement is not widely available.

20.76 Although very few AAGA cases in whom DOA monitoring had been used were reported to NAP5, distress and severe long term impact in these cases was sparse, suggesting that perhaps, the control of anaesthesia in these cases was, despite being associated with AAGA, not one that led to adverse outcome. This finding should inform future trials of the efficacy of DOA monitoring in reducing AAGA. Rather than study the effect of monitoring in an unselected cohort, it may be more appropriate to focus on specific groups (e.g. patients with neuromuscular blockade and receiving intravenous anaesthesia). Furthermore, a 'binary' view of AAGA may be erroneous and greater attention may need to be paid to the specific impact on patients who experience AAGA. Thus even if in a trial the overall incidence of AAGA is unaffected by pEEG monitoring, it would be important if it were found that this monitoring mitigates adverse impact.

20.77 In summary, the NAP5 data appears to offer no support to a recommendation of universal specific DOA monitoring. However, it identifies the use of neuromuscular blockade in any context as an important risk factor for AAGA, and DOA monitoring may have a role in this situation. Specifically, the combination of TIVA with neuromuscular blockade may confer the highest risk for AAGA, and it is in this cohort that the use of DOA monitoring appears to confer the greatest protection (a hypothesis that warrants formal investigation). If, however, technologies for specific DOA monitoring are to be more widely adopted and optimally used, there needs to be a more coherent approach to research, training and development of pragmatic guidelines than there has hitherto been.

The importance of, or correct response to, a brief rise in BIS values above 60 is not currently known



IMPLICATIONS FOR RESEARCH

Research Implication 20.1
There is considerable scope for research using the isolated forearm technique, with implications for both fundamental science and anaesthetic practice. One question is the degree to which a positive response is associated with later adverse impact; another is how the incidence of positive IFT response is influenced by specific anaesthetic drugs or techniques. Further research into IFT responses when standard (rather than lower than usual) anaesthetic drug doses are administered is also needed.

Research Implication 20.2
Research on DOA monitors should extend to study their use in the dynamic phases of general anaesthesia (induction and emergence).

Research Implication 20.3
Research should focus on developing pragmatic algorithms aiding the integration and interpretation of all information available relating to depth of anaesthesia. There should be particular focus on resolving dichotomies, e.g. where blood pressure or end-tidal levels indicate the depth should be 'light' but DOA monitoring indicates the reverse.

Research Implication 20.4
Clinical trials seeking to establish the efficacy of DOA monitoring could usefully focus on patients undergoing anaesthesia with neuromuscular blockade and with intravenous anaesthesia.

RECOMMENDATIONS

RECOMMENDATION 20.1
Anaesthetists should be familiar with the principles, use and interpretation of specific depth of anaesthesia monitoring techniques (i.e. the available EEG-based monitors and the isolated forearm technique). Relevant anaesthetic organisations should include this monitoring in their core training programs.

RECOMMENDATION 20.2
The relevant anaesthetic organisations should develop pragmatic protocols or algorithms for the use of all available information about depth of anaesthesia (including information from DOA to guide anaesthetic dosing.

RECOMMENDATION 20.3
Anaesthetists should recognise that neuromuscular blockade constitutes a particular risk for AAGA. Use of a specific form of depth of anaesthesia monitor (e.g. pEEG or IFT) is logical to reduce risk of AAGA in patients who are judged to have high risk of AAGA for other reasons, and in whom neuromuscular blockade is then used.

RECOMMENDATION 20.4
If specific depth of anaesthesia monitoring is to be used (e.g. pEEG or IFT) then it should logically commence, if feasible, before/at induction of anaesthesia and continue until it is known that the effect of the neuromuscular blocking drug has been reversed sufficiently.

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