

Neuromuscular blocking drugs



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HEADLINE

19.1. Slightly fewer than half (46%) of the general anaesthetics administered in the United Kingdom include the use of a neuromuscular blocking drug (NMB). However, almost all (97%) reports to NAP5 of certain or probable unintended awareness during planned general anaesthesia concerned patients who had received an NMB. The cases of 'accidental awareness during general anaesthesia' reported to NAP5 were therefore overwhelmingly cases of 'unintended awareness during paralysis'.

BACKGROUND

19.2 Neuromuscular blocking drugs (also commonly referred to as neuromuscular blockers, NMBs or 'muscle relaxants') are administered during general anaesthesia to block the transmission of signals between motor nerve endings and skeletal muscles, preventing the affected muscles from contracting and also reducing their resting tone. Thus NMBs paralyse/relax the jaw and the vocal cords facilitating laryngoscopy and tracheal intubation, and various other muscles (especially of the trunk) whose paralysis may facilitate artificial ventilation and surgery.

19.3 An unparalysed patient who is awake will have the capacity to move in response to unpleasant stimuli. Such movement can be used to indicate an inadequate depth of anaesthesia. However, patients may not be able to move if they are physically restrained (as is a common component of positioning and padding for safety during surgery). It has also been suggested that even without NMBs a patient may feel paralysed by a putative effect of anaesthetics on the basal ganglia (Devor & Salkind, 2001; Sukhotinsky et al., 2005).

19.4 However, when a neuromuscular blocking drug is given, the capacity to respond by movement (i.e. *motor capacity*) is impaired or abolished, and it becomes difficult 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, because 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).

19.5 There is good evidence that AAGA can, and does, occur in the absence of autonomic signs. Ghoneim et al. (2009) reviewed 271 cases of AAGA and reported that tachycardia was present in only 20% and hypertension in 18% of these cases. Patient movement was reported in 14%. Domino et al. (1999) reporting on a cohort of 61 medicolegal claims for AAGA (80% of which occurred during surgery) reported hypertension in 15%, tachycardia in 7% and patient movement in 1.5%.

- 19.6 The ‘anaesthetist’s dilemma’ of how to detect consciousness in a paralysed patient is to some extent shared with neurologists (dealing with persistent vegetative state or ‘locked-in’ syndromes; Pandit, 2013). In anaesthesia, where the paralysis is temporary and induced by the practitioner, the traditional solution in this dilemma is to give 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 an electronic depth of anaesthesia monitor or the isolated forearm technique, and this is discussed in Chapter 20, DOA.
- 19.7 Separately from the monitoring of the conscious level, it is also possible to monitor the degree of paralysis induced by neuromuscular blockade.
- 19.8 Because of the effect of NMBs on patients’ ability to communicate and move when aware, there is concern that NMBs predispose to AAGA and to the adverse effects of AAGA when it occurs (Sandin et al., 2000). Large randomised trials such as B-Aware (Myles et al., 2004) have predominantly studied patients in whom NMBs were administered. Other large trials have not explicitly recorded NMB as a

risk factor (B-Unaware/ BAG-RECALL; Avidan 2008 & 2011). In a prospective study of 11,785 patients (Sandin et al., 2000), the overall incidence of AAGA with NMB was 0.18%, compared with 0.1% when no NMB was administered. Furthermore, the adverse impact seemed greater when NMB was used: *‘Four non-paralysed patients recalled intra-operative events, but none had anxiety during wakefulness or had delayed neurotic symptoms. This finding contrasts with anaesthesia with muscle relaxants, during which 11 of 14 patients had pain, anxiety, or delayed neurotic symptoms.’*

NAP5 CASE REVIEW AND NUMERICAL ANALYSIS

- 19.9 The NAP5 Anaesthesia Activity Survey reported that NMB was used during 46% of general anaesthetics.
- 19.10 Neuromuscular blockade is dramatically over-represented in the cohort of AAGA reports (see also Chapter 6, Main Results). Table 19.1 shows in more detail the breakdown of data by Class of AAGA. Of 130 cases of Certain or probable awareness, ICU cases and Drug Errors, NMBs had been administered in 130 cases (97%).

Table 19.1. Proportion of NMB use in the different categories of AAGA

	NMB	No NMB	% NMB use in AAGA
Certain or probable awareness (Class A)	107	3	97%
Possible awareness (Class B)	24	7	77%
ICU cases (Class D)	6	0	100%
Syringe swaps/drug error/ other (Class G)	17	1	95%
Total	154	11	93%

- 19.11 The sparseness of results makes formal statistical comparison impossible between the cohort that received no NMB vs those that did. However, even the three cases of Certain/probable awareness in which an NMB had not been administered, generally resulted in a rather vague symptomatology. In these three cases and the one case of drug error where no NMB had been administered (Classes A and G), none of the patients reported pain or paralysis and the modified NPSA scores were judged to be None, Low, Moderate and Severe in one patient each.

Use of a muscle relaxant increases the risk of AAGA and of sensations of paralysis



19.12 The seven cases of possible AAGA without NMB were even vaguer reports (which in part led to their classification as 'Possible' rather than 'Probable').

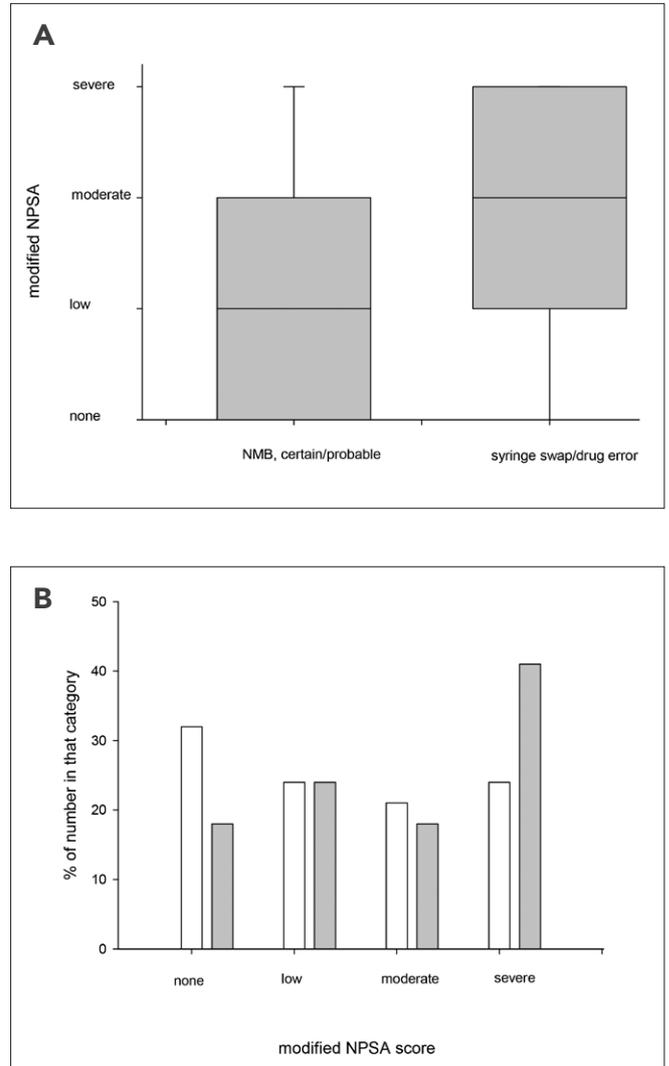
Anaesthesia was induced in a child with poor venous access in order to insert a central venous catheter. Intravenous induction was intended but the peripheral venous cannula tissued as propofol was being injected through it and induction was completed by inhalation of sevoflurane from a face mask. The child reported afterwards that he remembered the facemask application for a few seconds and did not like it.

An overweight elderly patient underwent orthopaedic joint surgery under a combined spinal and epidural anaesthetic. The patient breathed oxygen spontaneously through a simple Hudson-type face mask and 1% propofol was administered by infusion at 30-40 ml/h with no record of a bolus being administered. The patient reported expecting to be asleep but was aware of their leg being positioned before surgery and was distressed by this. The plan for anaesthesia had been documented as being 'CSE+GA' (i.e. combined spina-epidural plus general anaesthesia).

A young patient underwent minor surgery. Intravenous anaesthesia was induced and a laryngeal mask airway was inserted. The patient was transferred to the operating room where anaesthesia was maintained with isoflurane in oxygen and air. Before surgery, the patient sat up on the operating table and tried to grab the surgeon. Additional anaesthetic was rapidly given. The anaesthetist questioned the patient in the recovery room after surgery, who reported a dream in which he sat up in the operating theatre.

19.13 A comparison is possible of longer term psychological sequelae (using the modified NPSA scores) between those patients in the Certain/probable category who received NMBs (Table 19.1) and those patients in whom there were syringe swaps or drug errors. This latter group generally experienced paralysis without any hypnotic agent. Figure 19.1A shows that whereas the median score for the former was 'low' with 'severe' being a relatively infrequent consequence, for the latter, the median score was 'moderate', with 'no impact' being less common. Although this statistical analysis highlights the greater psychological morbidity in the patients with unmodified 'awake paralysis' (see Chapter 13, Drug Errors) modified NPSA scores were still 'severe' for 25% of Class A cases (Figure 19.1B).

Figure 19.1. (A) Boxplots of modified NPSA scores for Certain/probable patients who received NMB vs patients in whom drug error or syringe swaps led to accidental paralysis. (B) The same data plotted as bar charts of the % in the respective group exhibiting the degree of impact: white bars, Certain/probable cases; grey bars, syringe swaps/drug errors.



19.14 While most Certain/probable and ICU cases reported their experiences promptly, if all 11 reports of AAGA without NMB are considered there appears to have been considerable delay in reporting: a median of over three years with one patient reporting after almost 40 years (median 1,203 days (7 – 3,650 [0 – 14,158] days).

19.15 In contrast, in cases, where NMBs were administered, AAGA resulted in considerable distress. Distress at the time of the episode was reported in 51% of all reports where NMBs were used, in 61% when paralysis was also experienced and in 77% when both paralysis and pain were experienced.

An elderly patient underwent orthopaedic surgery with anaesthesia including NMB. On transfer to theatre volatile anaesthesia was unintentionally omitted. On surgical incision, hypertension was noticed and volatile re-commenced. On waking in recovery the patient reported having heard voices and experiencing severe pain: the knee 'opened up like a flower; there was a very strong pushing against the leg'. The patient tried to shout and move, but could not and then felt an extreme, sharp, agonising pain of a knife slicing into skin with flesh pulled apart, the patient felt paralysed and was terrified. The patient subsequently developed flashbacks and re-living experiences, and felt traumatised.

A young patient underwent an urgent abdominal surgery. On the anaesthetic chart the first drug documented as being given was an NMB followed by propofol. The patient clearly remembered the anaesthetist saying "oh dear that was muscle relaxant". The experience seemed to last for a long time before induction. The patient felt paralysed, unable to speak or move and feared death. The patient became terrified about future anaesthetics, with sleep disturbance and worry about death on a daily basis.

A young patient underwent anaesthesia for ENT surgery during which NMB was administered. When the patient awoke in the recovery room it appeared that the effect of the NMB had only been partly reversed and their muscles were still very weak. A further dose of reversal was given. "It was really horrible, I could hardly see them moving and talking around me, I was unable to talk or to move, I felt that my chest was too tight. I was very scared, I thought I will be paralysed and unable to move, it was really bad experience." The patient developed anxiety and fear about anaesthesia and flashbacks. The patient required psychological support.

- 19.16 Yet, not all patients experiencing 'awake paralysis' were distressed by the experience and if the patient understood the cause of the inability to move this may have reduced distress.

A young patient underwent an urgent general surgical procedure. A year later they reported that they had been aware during surgery, feeling paralysis and pain in the abdomen, and wanting to ask for pain relief. The patient also heard voices talking about drugs and saw bright lights through closed eyes. The paralysis was not a great worry as the patient knew 'you were supposed to be paralysed during the operation'.

- 19.17 An experience of paralysis associated with NMB during AAGA was not restricted to the maintenance (surgical) phase of anaesthesia: 24% of all Certain/probable and Possible reports described it at induction and 16% at emergence.
- 19.18 When unintended awareness during NMB was suspected by the anaesthetist, immediate verbal reassurance appeared to reduce the patient's distress.

A patient inadvertently was given suxamethonium before induction. The anaesthetist immediately recognised the error and induced anaesthesia. The patient experienced paralysis, was afraid they were dying from a stroke and had flashbacks for 2-3 days afterwards. However the patient was very reassured by the anaesthetist's immediate explanation, "I know what's happening and I can fix it", during the critical event, and had minimal long-term sequelae.

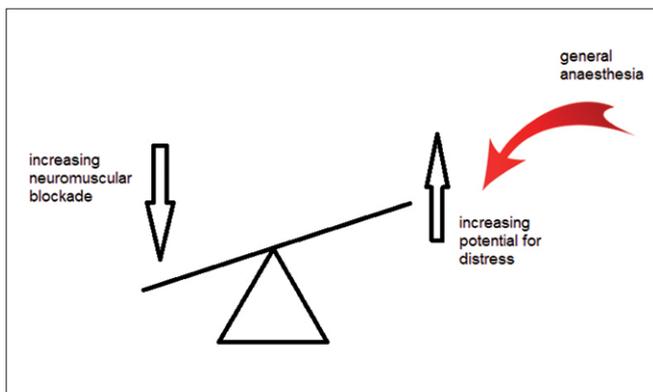
- 19.19 At emergence, AAGA was generally caused by mistimed or mismanaged NMB, failure to monitor the effects of NMB and failure to consider idiosyncratic responses to single doses of NMBs. These reports are discussed in Chapter 10, Emergence.

DISCUSSION

- 19.20 The vast majority of NAP5 reports were of unintended awareness during neuromuscular blockade. Indeed, 'unintended awareness during neuromuscular blockade' may be a better term than unintended awareness during general anaesthesia to describe the principal problem reported to NAP5. There were over twice as many patient reports of paralysis alone (59) than pain alone (26).
- 19.21 Furthermore, the majority (61%) of patients who experienced paralysis were distressed. Descriptions suggest that this was probably because they could not rationalise an entirely novel experience. Distress at the time of the episode appears to be an important factor in determining longer term adverse effects (Chapter 6, Main Results and discussion in Chapter 7 Patient Experiences).
- 19.22 The anaesthetist who administers a neuromuscular blocking drug assumes a great responsibility for ensuring the patient's welfare. Physiologically, the patient will die within minutes unless the airway and ventilation are adequately maintained. Psychologically, it is essential to ensure unconsciousness during paralysis.

- 19.23 Two-thirds of the cases of unintended awareness during NMB reported to NAP5 occurred before or after rather than during surgery. Even a very brief (seconds) episode of paralysis sometimes led to severe distress and long-lasting psychological sequelae. Any case in which neuromuscular blockade is used must be regarded as carrying increased risk of AAGA.
- 19.24 Conceptually, unopposed global neuromuscular blockade might be imagined as an intervention with capacity to cause great psychological harm, unless it is counteracted by general anaesthesia (Figure 19.2).

Figure 19.2. Diagrammatic representation of the balance between neuromuscular blockade and distress, the latter ameliorated by general anaesthesia. When the 'seesaw' is balanced (in neutral position) there is no neuromuscular blockade and no distress



- 19.25 In support of the above model, it is notable that the group of patients who experienced the worst psychological sequelae after AAGA were those who experienced awake paralysis without any co-administration of anaesthetic drugs. This was the group of patients who were administered NMB before intended anaesthesia due to syringe swap/ drug error (see Chapter 13, Drug Errors).
- 19.26 Disruption of the balance of Figure 19.1 by unopposed neuromuscular blockade can occur at any time during anaesthesia. Thus NAP5 contains reports of paralysis at induction, on transfer into theatre, during surgery, during transfer from theatre, and during recovery.
- 19.27 Reflecting on these reports of AAGA, it can be argued that the main 'purpose' of general anaesthesia is not really to manage the pain of surgery. Pain can clearly be very effectively and separately controlled by analgesics or regional anaesthesia, and many operations are conducted with the patient awake. Rather, general anaesthesia is an essential condition to allow patients to tolerate the global paralysis that is required for

some surgical procedures. Whereas it is eminently possible for pain to be well managed in an awake patient, it would seem rare for awake patients to tolerate even modest periods of complete paralysis. Adopting this view of the purpose of general anaesthesia would help underline the importance of global paralysis in an awake patient.

IMPLICATIONS FOR RESEARCH

Research Implication 19.1

Further research into development of reliable sensitive and specific means of detecting AAGA during paralysis would be of benefit to patients.

Research Implication 19.2

It would be important for research to develop a model to explain the psychological response to different degrees of global paralysis during anaesthesia (and in comparison to other circumstances).

Research Implication 19.3

It is worth investigating the hypothesis that patient responses differ to different degrees of paralysis in different limbs or parts of the body (e.g. those induced either by neuromuscular blockade, or regional anaesthesia, or disease).

RECOMMENDATIONS

RECOMMENDATION 19.1

Given the potentially serious consequences of paralysis unopposed by general anaesthesia even for brief periods, anaesthetists should plan the use of neuromuscular blockade very carefully; assessing whether it is needed at all, if so then whether needed throughout surgery, and to what depth of blockade.

RECOMMENDATION 19.2

Care should be exercised in the handling of syringes of neuromuscular blocking drugs prepared 'in case' of need: inadvertent administration may have catastrophic results.

RECOMMENDATION 19.3

If neuromuscular blockade is planned, then anaesthetists should ensure consent, and that explanation outlines the possibility of feeling weak or unable to move, for example at the start or end of the anaesthetic.

RECOMMENDATION 19.4

If AAGA is suspected, immediate verbal reassurance should be given during the episode to minimise adverse consequences, as well as additional anaesthetic to limit the duration of the experience.

RECOMMENDATION 19.5

Anaesthetists should minimise the risk of any period of neuromuscular blockade without anaesthesia by the appropriate use of a nerve stimulator coupled with end-tidal volatile agent monitoring. Where the latter is absent or irrelevant (such as in TIVA), then specific depth of anaesthesia monitoring may be necessary.

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