Memory and awareness during anaesthesia

Editor—I could not help noticing that not a single word can be found about the role of neuromuscular blockers in awareness under anaesthesia in either the editorial1 or in the abstracts of the 7th International Symposium on Memory and Awareness in Anaesthesia published in the June issue of the journal.2 Predictably, little progress has been made in the last 10 yr in tackling the problem of awareness under anaesthesia and skeletal muscle movement continues to be the ‘gold standard’ for detection of this embarrassing complication. However, it is apparent from what appears in the literature that the opinion formers and possibly those providing the specialist training have largely ignored many attempts, including mine in 1995,3 to alert the profession for the misuse of neuromuscular blockers. Perhaps, there is a positive side to the persistence in practice of this avoidable complication: it provides a powerful stimulus for the research into the mechanisms of anaesthesia and memory formation.

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Editor—We read with interest the editorial by Sneyd and Matthews1 and in particular their comments on the recent B-Unaware trial and the use of nitrous oxide. Although we agree with their assertion that ‘the additivity of MAC fractions of nitrous oxide and inhalation agents for the suppression of reflex responses is well recognized, their interaction on memory formation is less clear and cannot be assumed to be additive’, the information from the B-Unaware trial suggests that the interaction of nitrous oxide and volatile, if anything, may have a more than additive effect on memory.4 It is striking that none of the patients in the ‘definite’ or ‘possible’ awareness groups in B-Unaware was treated with nitrous oxide. Indeed, one possible message from this trial might be that the use of a BIS- or end-tidal anaesthetic gas (ETAG)-guided volatile protocol in combination with nitrous oxide could reduce the incidence of awareness in (relatively) high-risk patients to zero! This finding is in contrast to those of Myles and colleagues5 in the ENIGMA trial, which showed a non-significant trend towards increased awareness in the nitrous oxide-treated group. This finding from B-Unaware may be hypothesis-generating for future trials examining awareness using volatile with or without nitrous oxide.

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Editor—In their editorial, Sneyd and Mathews1 state ‘The investigators [B-Unaware trial]4 have shown that both awareness risk-reduction strategies, BIS monitoring, or care by anaesthetic protocol, work equally well.’ In doing so, they effectively draw two conclusions from that trial, both of which are unsupported after close scrutiny of the experimental methodology. The first conclusion, one reached neither by the investigators themselves nor in the editorial accompanying their paper,6 is that the overall incidence of awareness in the study patients was lower than it would have been had the two strategies not been used. The observed incidence was 0.21%, similar to that seen in other studies of the general population.7,8

Sneyd and Mathews assume a ‘real’ incidence of awareness of 1% in the B-Unaware patients—an assumption shared, at least initially, by the trial investigators. This expectation is ill-founded. According to the investigators, it is based on two trials relating specifically to anaesthesia for cardiac surgery—in which 3/2049 and 8/70010 patients, respectively, reported awareness—together with the incidence observed in unmonitored patients in the B-Aware trial, namely 11/1238.11 The proportion of patients in the B-Unaware trial undergoing any type of heart surgery is not reported, but many of the patients were recruited according to the criteria not used in the B-Aware trial, including daily alcohol consumption, ASA class IV–V, and marginal exercise tolerance, respectively, accounting for 18%, 22%, and 38% of all patients.

There is good reason to suppose that these new B-Unaware criteria for high awareness risk are much less stringent than those in the B-Aware trial. Although chronic alcoholism has been shown to increase anaesthetic requirements,12 the effects of daily alcohol consumption are unknown. In their study of 19575 patients, Sebel and colleagues7 used multiple regression to determine that ASA class III–V patients were more at risk of awareness than ASA I–II patients (OR 2.85; 95% CI 1.29–6.28). However, of the 25 patients reporting awareness, 12 were ASA class III (out of 5093 ASA III patients) and two were class IV or V patients (out of 880). Had the authors restricted their analysis to ASA classes IV–V alone, the inclusion criterion later used in the B-Unaware trial, it is unclear whether high ASA class would still have been identified as an independent risk factor for awareness. Uncertainty on this issue is compounded by Domino and
colleagues'\textsuperscript{13} review of closed claims relating to awareness, in which no significant association between ASA class and awareness risk was found. As for marginal exercise tolerance, I can find no evidence for this being independently associated with a high risk of awareness.

Use of these new, weaker criteria in the B-Unaware trial is likely to have reduced the overall incidence of awareness from the 1\% seen in the B-Aware trial to a lower figure, quite possibly identical to the one actually seen. In other words, the observed incidence of 0.21\% may not represent a reduction, consequent on anaesthetic technique, from some hypothetical baseline but merely the effect of choosing patients with different characteristics.

Leaving aside whether the two B-Unaware strategies have any effect on awareness at all, Sneyd and Mathews further conclude that the incidence of awareness in the two groups is the same. This is incorrect. The study’s \textit{a priori} power calculations were based on an anticipated 1\% incidence of awareness in the ETAG group and 0.1\% for the BIS group. With these figures, a total of 940 patients are required in each group to detect a 0.9\% difference with a one-tailed alpha of 0.05 and a power of 80\%. Online statistical software\textsuperscript{14} conveniently allows both reproduction of the original calculation and recalculation using the actual, rather than the predicted, incidence of awareness. This indicates that to detect a between-group difference in awareness proportional to the one the investigators sought (i.e. from 0.21\% to 0.021\%), the B-Unaware sample size would have provided just 4\% power.

The adequately powered B-Aware study established that BIS-guided anaesthesia reduces the incidence of intraoperative awareness in patients genuinely at risk from this complication. The inadvertently underpowered B-Unaware study gives few grounds to doubt this finding, or to assert the equivalence with BIS monitoring of any anaesthesia delivery protocol. Whether we are inclined to B-Aware or to B-Unaware, careful examination of the evidence is always advisable lest our conclusions B-Unjustified.

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Editor—I am grateful for the interest and comments on the published Abstracts from the recent Memory and Awareness, MAA7 meeting,\textsuperscript{2} and the accompanying editorial.\textsuperscript{1}

Dr Ponte is right to be concerned about the lack of attention to the possible role of neuromuscular blockers in awareness. A recent study from Spain described an incidence of awareness of 1\%, and all 39 patients with conscious awareness had received neuromuscular blocking agents.\textsuperscript{15} However, it is probably more appropriate to take issue with the research community rather than with those writing editorials—we can only report that which we see and hear. In fact, the MAA7 meeting did again contain mention of the isolated forearm technique. It remains likely that a proportion of cases of awareness could be avoided by the general adoption of relaxant-free techniques.

Regarding nitrous oxide, Drs Lynch and Grant have themselves pointed out the incidence of awareness in patients randomized to nitrous oxide in the ENIGMA\textsuperscript{5} study, so the lack of nitrous oxide in the patients with awareness in the B-Unaware study\textsuperscript{4} may simply be a coincidence. The key issue is the lack of data. How different MAC fractions of inhalation agents and nitrous oxide do or do not combine to prevent awareness remains unclear. Only a study with patients randomized to equi-MAC anaesthetics with and without nitrous oxide can definitively resolve this.

Dr Morley takes the issue with the assumed awareness risk of 1\% in high-risk patients—this was proposed by the B-Unaware authors\textsuperscript{4} on the basis of three published studies. The B-Unaware study comprised two intervention groups [BIS-guided anaesthesia and a protocol based on a measurement of end-tidal anaesthetic gases (ETAG) anaesthesia]. In the absence of any ‘standard anaesthesia’ group, we can only speculate about what the baseline risk of awareness might have been. Perhaps 1\% if we accept that the patients were indeed ‘high risk’—or perhaps less if we accept Dr Morley’s critique of the inclusion criteria. Since we do not know what the baseline risk was, it is indeed true that both BIS and ETAG may be either very effective or entirely ineffective, but crucially, they were equally so. It is also important to recognize that if the baseline incidence of awareness is low, that is, nearer 0.2\% than 1\%, then the B-Unaware study was underpowered to resolve the differences between the two techniques. This does not make BIS a better technique than ETAG—it just leaves us uncertain.

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1 Sneyd JR, Mathews DM. Memory and awareness during anaesthesia. Br J Anaesth 2008; 100: 742–4
3 Ponte J. Neuromuscular blockers during general anaesthesia: less may be better. Br Med J 1995; 310: 1218–9
Editor—We were interested to read the study by Errando and colleagues describing their experience of awareness with recall (AWR). While the figure of 1% is undoubtedly concerning, there are multiple methodological problems with their paper, which may influence the results, and limit any conclusions to be drawn from it.

We note the audit commenced in 1995, but was not completed until 2001 after recruiting only 4001 patients. Does this reflect that the population was merely a sample and therefore subject to potential sampling bias. Can the authors explain the role that ASPECT Medical Systems had in this project? Was the project actually studying the way anaesthesia was delivered over this period? We note the anaesthetic techniques described in their paper contained some with a high likelihood of awareness. As such, the results may lack external validity because their findings may be non-representative. There are also discrepancies in totals within their tabulated data, which have not been adequately explained.

We performed an almost identical prospective audit in an Australian tertiary referral hospital in 2001 but found a much lower incidence of awareness. Our figures were in keeping with the established literature discussed in a recent editorial in this journal. A research nurse interviewed every consecutive surgical patient operated on in our institution during a full 12 month period. Data were collected on 5371 patients of whom 4899 received general anaesthesia. Using the same definition as Errando and colleagues, we had two cases of AWR-yes making our incidence of intraoperative awareness 0.04% (95% confidence interval 0–0.1%). Both cases occurred during balanced general anaesthesia with volatile agents. Since we interviewed consecutive patients in a full 12 month period, our incidence of 0.04% is a true rate of awareness in our institution. The techniques used in our hospital for general anaesthesia during the audit period were balanced anaesthesia (87%) and total i.v. anaesthesia (13%). No anaesthetist was using solely O2/N2O for maintenance.

Both of these audits were performed during a similar time period over 7 yr ago. We can only speculate why the incidences are so different. We suggest the validity of their results be considered in the light of these points.

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Awareness and anaesthesia

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Editor—Thank you for your interest in our article on AWR during general anaesthesia. Some of the suggested methodological problems in our work are discussed in our article. In addition, space constraints in this type of article (data rich) preclude the inclusion of all the information and this can introduce apparent biases. The timescale of patient recruitment, and the number of patients involved, was described in the Methods section. To extend the explanation, we blindly recruited patients in the post-anaesthesia care unit (PACU) (4–8 per day) on the days a participating anaesthetist was available. Unfortunately, our PACU was closed due to staff shortages for 1.5 yr. Thus, the patients were consecutively recruited, but not all patients anaesthetized during these years were entered in the database (20 000 patients per year anaesthetized in our hospital). No other considerations were taken into account in recruiting and we did not consider this as ‘sampling’.

The participation of a member of Aspect MS was declared on submission of the manuscript. At the time the study was performed, BIS was not available to us. Dr Sigl’s participation was in the post-retrieval analysis of the data, contribution in the explanation of the findings related with this, and participation in the ‘discussion’ related to these aspects. There was no influence on the anaesthetic techniques, and the anaesthetist in charge was free to choose premedication, anaesthetic technique, drugs, and doses. The variety of anaesthetic techniques can be explained, in part, by the different anaesthesia training of the doctors, and because, at that time, we had a non-standardized method of work at our hospital.

I congratulate the authors for their low incidence of AWR, but, in my opinion, the way and timing of the patient’s interview, together with the definition of AWR, are both important. Comparison with the paper by Hennessy and colleagues is not possible as it is an Abstract without complete information. Finally, as stated in our Discussion, the true figures of AWR quoted in the recent, large studies may need to be increased by a factor of 2–3 if the definition of AWR used in our study, or if ‘possible’ awareness cases, had been included.