CHAPTER
6

NAP5 summary of main findings and incidences


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HEADLINE

6.1 The estimated incidence of patient reports of AAGA (using a parallel national anaesthetic Activity Survey to provide denominator data) for Certain/probable and Possible cases of AAGA was ~1:20,000 anaesthetics. However, there was considerable variation in this incidence when subtypes of anaesthetic techniques or subspecialties were taken into account. Thus, whereas the incidence of reports of AAGA when neuromuscular blockade was used was ~1:8,000, when no paralysis was involved this was ~1:136,000. The cases of 'AAGA' reported to NAP5 were overwhelmingly, cases of unintended awareness during neuromuscular blockade. The incidence of reports from cardiothoracic anaesthesia (~1:8,600) closely resembled that for neuromuscular blockade. The incidence of reports of AAGA after general anaesthetic Caesarean section was much higher, ~1:670. Almost two-thirds of AAGA experiences arose in the dynamic phases of anaesthesia (at induction and emergence). One third of AAGA events arose during the maintenance phase of anaesthesia. There was an over-representation in AAGA cases (versus the population of general anaesthetics as estimated by the Activity Survey) of: neuromuscular blockade (associated with under-representation of use of a nerve stimulator or reversal of blockade), thiopental, rapid-sequence induction, total intravenous anaesthesia techniques, female patients, early middle age adults, out of hours operating, junior anaesthetists, previous episodes of AAGA and specific depth of anaesthesia monitoring. Many of these warrant further detailed exploration. Paediatric cases, trauma and orthopaedics and plastics were under-represented.

BACKGROUND

6.2 NAP5 is probably the largest and most comprehensive study AAGA and its risk factors ever undertaken.

6.3 Perhaps the most common tool used to establish the incidence of AAGA has been the Brice interview, conducted immediately after surgery and often repeated up to three times over up to a month (Brice et al., 1970). Over several decades, the incidence appears to have been consistently reported to be ~1–2 :1,000 general anaesthetics (Sandin et al., 2000; Wennerrvirta et al., 2002; Myles et al., 2004; Sebel et al., 2004; Avidan et al., 2008 & 2011). It has been reported as higher in obstetric (1:384; Paech et al., 2008), cardiac (~1:43; Ranta et al., 2002) and paediatric (1:135; Davidson et al., 2011) anaesthesia. However, some studies do report a much lower incidence (1:14,560; Pollard et al., 2007) but have been criticised for using a modified Brice interview confined to within 48-hour of surgery (Leslie, 2007).

6.4 Interestingly, the NAP5 Baseline Survey also reported an 'incidence' for (patient reports of) AAGA of ~1: 15,000 (similar to the findings of Pollard et al., 2007). This was a national survey of

>8,000 senior anaesthetists in the UK and they were simply asked to state how many new cases of AAGA they had experienced in the calendar year 2011 (Pandit et al., 2013a and b). A similar survey conducted in Ireland (using as denominator an estimate of anaesthetic activity that was conducted in parallel (Jonker et al., 2014a) has also established an incidence for AAGA as reported to anaesthetists of ~1:23,000 (Jonker et al., 2014b). These surveys suffer from various limitations (as discussed in the relevant papers) including failure of patients to report the event, memory of the anaesthetist for the incident, biasing (i.e. anaesthetists perhaps failing to report) and also possible systems failures that prevent transmission of a patient report made to another practitioner back to the anaesthetist (Avidan & Mashour, 2013a and b).

6.5 Incidence apart, previous studies have also addressed factors which may be associated with AAGA. The possible influence of types of surgery (notably obstetric, cardiac and paediatric) has been mentioned above, and these may be related to specific anaesthetic practices (some of them arguably historical) that predisposed to AAGA. Anecdotally, risks may be conferred by the (historic) technique of avoiding volatile agent before (or perhaps more recently, after) delivery in obstetrics, or the use of cardiac bypass and largely opioid-based techniques for cardiac surgery.

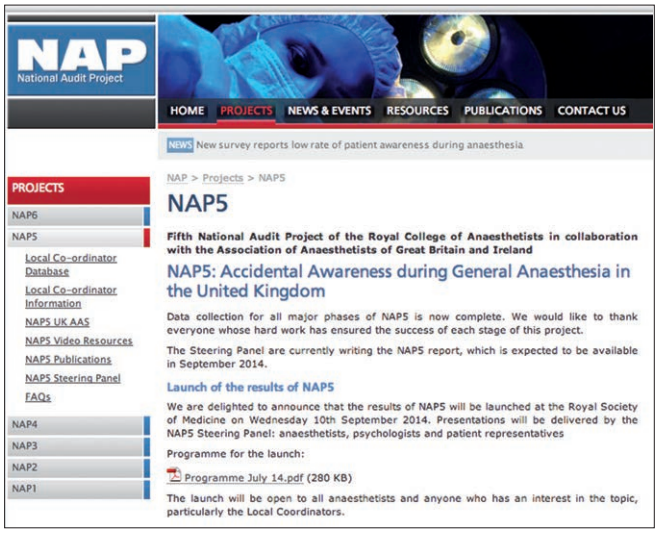
6.6 The obstetric influence may overall make AAGA commoner in women. Analyses of case series in medicolegal settings of awareness in the UK and the USA have demonstrated that a higher proportion of claims come from women. Domino et al., (1999) reported 77% of US claims were from women. Mihai et al., (2009) reported that 74% of UK claims were from women, and that 29% of claims arose in obstetric general anaesthesia. This may indicate that gender influences reporting rates as well as susceptibility to AAGA.

6.7 Some studies have reported that patients with a higher ASA score, are at increased risk of AAGA (Bogetz & Katz, 1984; Domino et al., 1999). Intentionally reduced doses of anaesthetic drugs because of concerns over cardiovascular and other effects may contribute to this. However, others find the converse; i.e. that patients with higher ASA scores are more susceptible to anaesthetic effects with lower AAGA incidence (Ranta et al., 1997).

6.8 There are several reasons why obesity is implicated in AAGA (Aranake et al., 2013). Inadequate drug dosing may arise because of the altered pharmacokinetics due to changes in body fat content, lean body mass, blood volume, cardiac output, total body water and alterations in plasma protein binding (Ingrande & Lemmens, 2010). However, some studies fail to find an association (Ranta et al., 1997; Ghoneim et al., 2009). Obesity is possibly associated with a difficult airway, which could potentially increase risk of AAGA, but Ghoneim et al., (2009) did not report this as a risk.

6.9 The notion of an intrinsic (possibly genetic) resistance to anaesthesia has been raised over the years in the literature. Ghoneim et al. (2007) reported that 1.6% of patients reporting AAGA described a previous history of AAGA. In the BAG-RECALL study, 11% of patients with AAGA had a previous history (Avidan et al., 2011). In most epidemiological studies of AAGA, cases are reported with no apparent cause (Errando et al., 2008; Sandin et al., 2000). Most recently Aranake et al., (2013) reported a secondary analysis of 26,490 patients enrolled in three major trials (B-Unaware, BAG-RECALL and MACS), and found that patients with a history of AAGA had a 5-fold greater incidence of AAGA. The Australian and New Zealand College of Anaesthetists has begun a collaborative trial to examine a possible genetic link to AAGA (see: (www.med.monash.edu.au/sphpm/anzca/research.html).

NAP website



NAP5 CASE REVIEW AND NUMERICAL ANALYSIS

6.10 Table 6.1 shows that by class of report, Certain/probable (Class A) were the commonest. Together with Possible (Class B), Sedation cases (Class C), ICU cases (Class D) and Drug Errors (Class G) this meant that the vast majority of reports likely had a genuine basis that was potentially confirmable.

Table 6.1. Numbers of reports by class

Class	Number of reports (%)
Certain/probable (A)	110 (37)
Possible (B)	31 (10)
Sedation (C)	32 (11)
ICU (D)	6 (2)
Unassessable (E)	19 (6)
Unlikely (F)	12 (4)
Swaps/drug error (G)	20 (7)
Statement Only (SO)	70 (23)
Total	300

6.11 Most of the data that are presented in this chapter focus on the 141 Certain/probable and Possible cases (Class A and B) combined.

Patient characteristics

6.12 Figure 6.1 shows the main patient characteristics in the Certain/probable or Possible cases, namely age distribution, body habitus and ASA grade, and their comparison with the distributions from the NAP5 Activity Survey. There appeared a marked under-representation of children (a 4.6-fold difference) and a slight over-representation of younger/middle-aged adults in AAGA reports, and an under-representation of the elderly. There was a preponderance of females reporting AAGA (65% vs 35% males) exceeding that in the Activity Survey (53% vs 47% males undergoing general anaesthesia). There is an over-representation of the obese in cases of AAGA in this category, with proportionately more than three times as many obese patients experiencing AAGA as undergo anaesthesia. The distribution of ASA grades in this category was in proportion with the numbers of patients undergoing general anaesthesia in the Activity Survey, with the majority of cases being ASA 1 and 2.

6.13 Tables 6.2 and 6.3 show some of the data used for Figure 6.1.

Figure 6.1. (A) Age distribution (The x-axis is in deciles, with the smallest value <5yrs and the largest >90 yrs); (B) ASA grades distribution; (C) body habitus distribution. Where a bar extends above the line that feature is relatively over-represented in the reported cases relative to Activity Survey activity – and vice versa

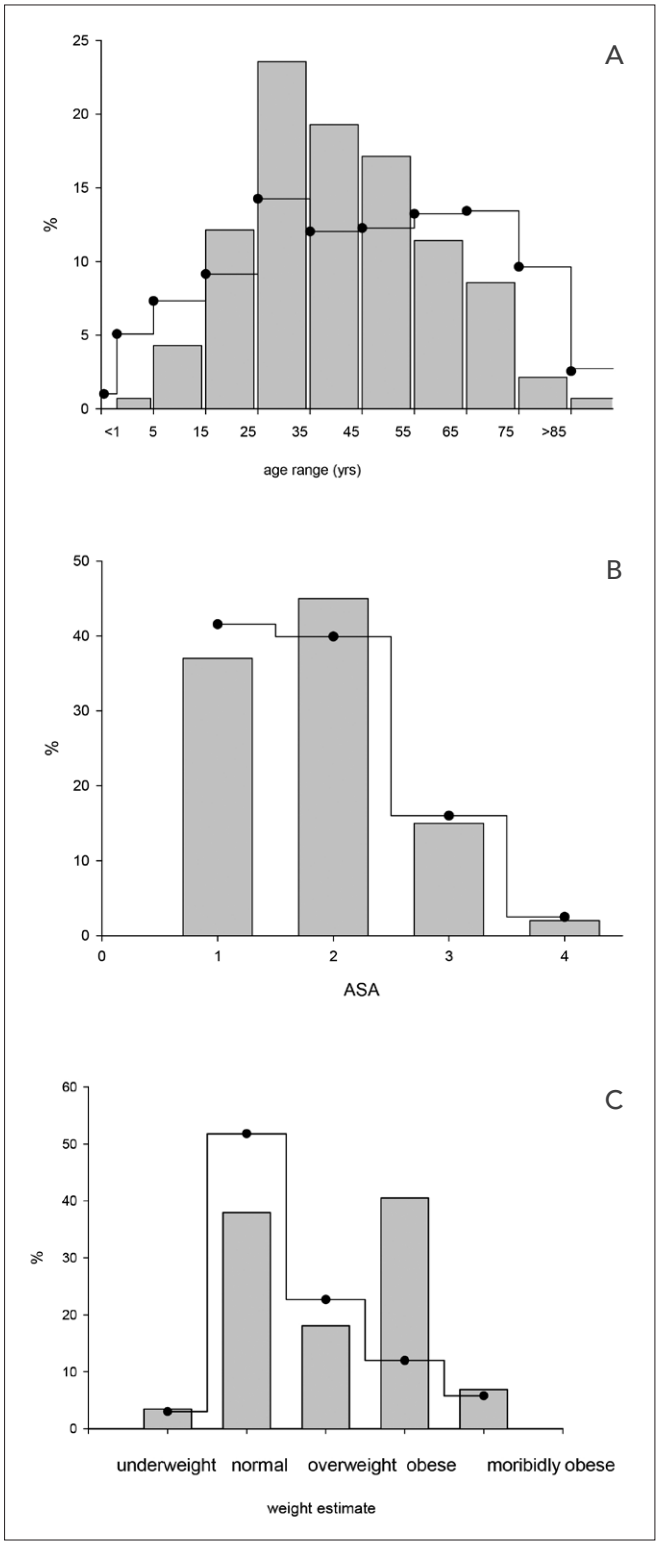


Table 6.2. Data used in Figure 6.1C for body habitus. A ratio >1 indicates the feature is over-represented in the cases relative to Activity Survey activity

Body habitus	% in Activity Survey	% in AAGA cohort	Ratio of % in AAGA cohort: Activity Survey
Underweight	3.00	3.4	1.15
Normal	51.8	37.9	0.73
Overweight	22.7	18.1	0.80
Obese	12.0	40.5	3.38
Morbidly obese	5.8	6.9	1.18

Table 6.3. Data used in Figure 6.1B for ASA distributions. A ratio >1 indicates the feature is over-represented in the cases relative to Activity Survey activity

ASA	% in Activity Survey	% in AAGA cohort	Ratio of % in AAGA cohort: Activity Survey
1	40.6	37.0	0.91
2	39.0	45.0	1.15
3	16.1	15.0	0.93
4	2.6	2.0	0.77

AAGA by specialty

6.14 By specialty (Figure 6.2), the striking result is the marked over-representation in AAGA cases of obstetrics (a 10-fold difference) and of cardiothoracic (2.5-fold difference). Two specialties appear 'under-represented' in AAGA cases: orthopaedics/ trauma/ spine (~1.5 fold difference) and plastics (a 5-fold difference).

6.15 Table 6.4 shows the data for Figure 6.2.

Figure 6.2. Distribution by specialty of Certain/probable and Possible AAGA cases (bars) and in the Activity Survey (dots and line). Three AAGA cases in bariatric and transplant surgery have been omitted as they were not sought in the Activity Survey. (ENT – ear, nose, throat and dental and maxillofacial surgery; ortho/ spine includes orthopaedics, trauma and spinal surgery; eye is ophthalmology; X-ray is radiology). General surgery includes urology and other specialties not listed

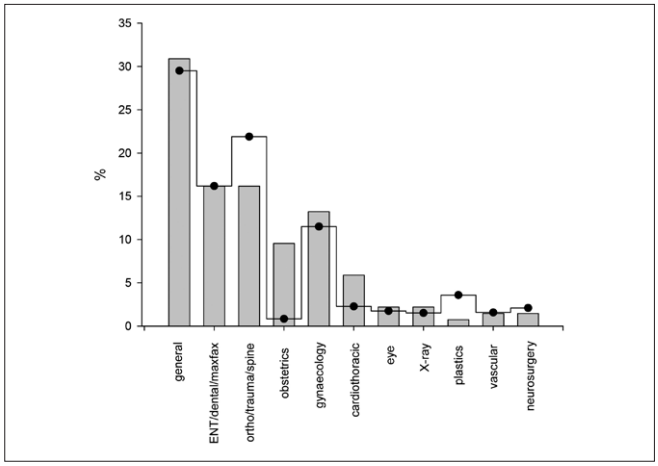


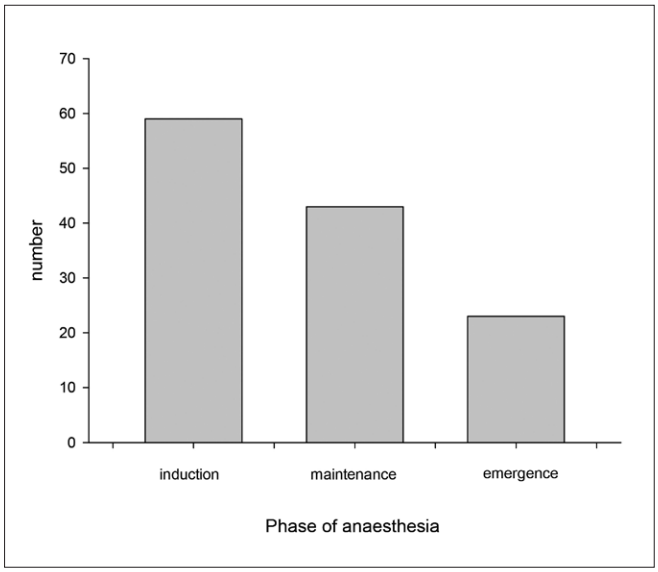
Table 6.4. Data used in Figure 6.2 for AAGA cases by specialty. A ratio >1 indicates the feature is over-represented in the cases relative to Activity Survey activity

Specialty	% cases in Activity Survey	% cases in AAGA cohort	Ratio of % cases in AAGA cohort: Activity Survey
General	29.5	30.9	1.04
ENT	16.2	16.2	1.00
Orthopaedic	22.0	16.2	0.74
Obstetrics	0.83	9.6	11.51
Gynaecology	11.5	13.2	1.15
Cardiothoracic	2.29	5.9	2.57
Ophthalmology	1.75	2.2	1.26
Radiology	1.53	2.2	1.44
Plastics	3.59	0.7	0.20
Vascular	1.59	1.5	0.92
Neurosurgery	2.1	1.5	0.70

AAGA by phase of anaesthesia

6.16 Two-thirds of Certain/probable and Possible reports were related to the dynamic phases of anaesthesia (induction n = 59 (47%) and emergence n = 23 (18%); Figure 6.3) compared with during maintenance n = 43 (34%). In nine cases AAGA was judged to occur during multiple phases and in seven cases the Panel was not able to judge a phase of occurrence.

Figure 6.3. Distribution of the cases by phase of anaesthesia (AAGA more common at induction > surgery > emergence)



Elements of anaesthesia practice and AAGA

6.17 The main features of anaesthetic practice in the AAGA cases compared with those in the Activity Survey are shown in Figure 6.4 and the corresponding ratios of occurrence of those variables in the AAGA cohort versus those in the Activity Survey in Figure 6.5.

6.18 Table 6.5 shows the data for Figures 6.4 and 6.5.

Figure 6.4. The representation of some components of anaesthesia practice in Certain/probable and Possible AAGA reports (bars) and in the Activity Survey (dots and lines). 'Propofol' in first bar refers to its use as an induction agent, as distinct from a later bar (TIVA/TCI) where its use is referred to for maintenance. N2O, nitrous oxide; NMB, neuromuscular blockade, RSI rapid sequence induction, DOA, specific depth of anaesthesia monitor

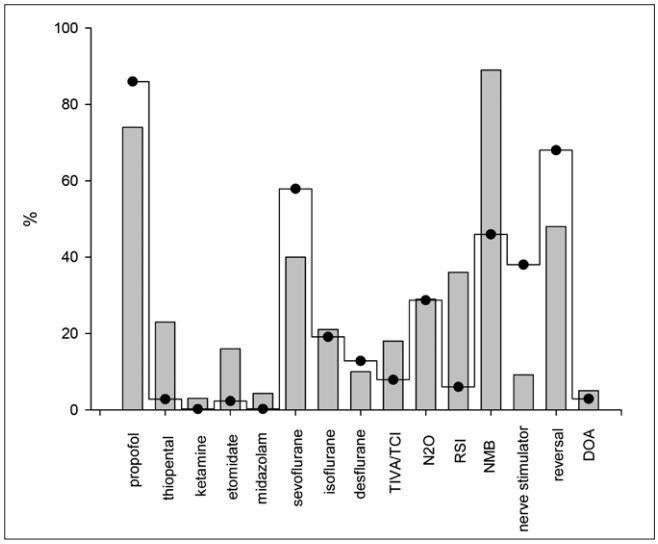


Figure 6.5. Ratio of the proportions from Figure 6.4 for each aspect of anaesthesia care. The horizontal dotted line at unity indicates the proportions being equal. The larger the bar, the greater is the feature represented in AAGA report; the smaller the bar, the less is the feature represented in the AAGA reports

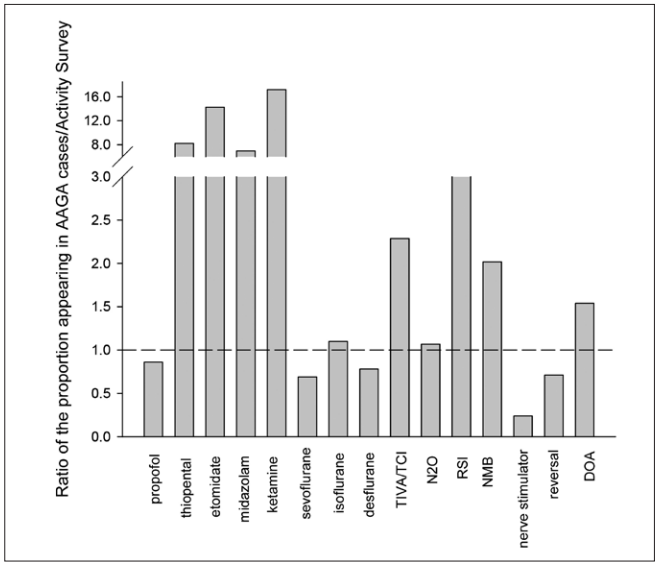


Table 6.5. Data used in Figures 6.4 and Figure 6.5. *for those cases in which non-depolarizing NMB used. A ratio >1 indicates the feature is over-represented in the cases relative to Activity Survey activity

Anaesthetic variable	% use in Activity Survey	% use in AAGA cohort	Ratio of use in AAGA cohort: Activity Survey
Propofol	86.0	74.0	0.9
Thiopental	2.8	23.0	8.2
Etomidate	0.2	3.0	14.3
Midazolam	2.3	16.0	7.0
Ketamine	0.3	4.3	17.2
Sevoflurane	57.9	40.0	0.7
Isoflurane	19.1	21.0	1.1
Desflurane	12.8	10.0	0.8
TIVA	7.9	18.0	2.3
N2O	28.7	29.0	1.1
RSI	36.0	6.0	6.0
NMB	46.0	93.0	2.0
Nerve stimulator*	38.0	9.2	0.5
Reversal of NMB*	68.0	48.0	1.7
DOA	2.8	4.3	1.5

6.19 Strikingly, neuromuscular blockade (NMB) appears far more commonly in the AAGA reports (93% of reports) than its use in general anaesthesia (in 46% of anaesthetics). Additionally, a nerve stimulator was used after a non-depolarising NMB much less frequently in AAGA cases (9%) compared with the Activity Survey (38%). Similarly, reversal of non-depolarising NMB was less common in AAGA cases (48%) than in the Activity Survey (68%). Thus the combination of using NMB, not monitoring its effect, and not reversing it together seemed to incur a risk for AAGA.

6.20 Of induction agents, thiopental, etomidate, midazolam and ketamine are over-represented in AAGA cases. Thiopental is used in only 3% of inductions in the Activity Survey, but features in 23% of AAGA reports – an almost 8-fold difference. Fewer cases overall were conducted with the other three agents, making them subject to greater variation in estimates (and the Activity Survey did not differentiate between co-inductions or use of midazolam or ketamine), so these data should be interpreted with caution.

6.21 Of the maintenance agents, the volatiles appeared in AAGA cases in broad proportion to their general use (although sevoflurane is somewhat under-

represented). Total intravenous anaesthesia (TIVA) when including all methods (i.e. target controlled infusions, manually varied infusions, fixed rate infusions and boluses) appears over-represented (18% in AAGA cases, but 8% overall; a greater than two-fold difference). Nitrous oxide is no less frequently used in AAGA cases than in cases overall.

6.22 Specific (EEG-based) depth of anaesthesia monitoring was used sparsely, but more commonly in the AAGA reports (4.3%) than in the general population of anaesthetics (2.8%). This is discussed in more detail in Chapter 20.

Incidence of AAGA reports

6.23 The Activity Survey indicates there were ~2,800,000 cases of general anaesthesia annually. The overall headline incidence of patient reports of AAGA can be estimated. Several incidences can be calculated depending on which cases of AAGA are included or excluded – for completeness and clarity we describe several. Discounting the Sedation cases, Unassessable and Unlikely reports, and the Statement Only cases (but including the Drug Error and ICU cases) leaves 167 cases; yielding an incidence of patient reports of AAGA ~1: 17,000 (0.006%) general anaesthetics.

6.24 If drug swaps are excluded (as they are really examples of unintended paralysis rather than accidental awareness) this leaves 147 cases and an incidence of patient reports of 1:19,000 (0.005%). Both the number and the estimated incidence is remarkably close to the estimate from the Baseline Survey of 153 cases and ~1:15,000, respectively. The incidence using only Certain/probable and Possible reports is 1 in 20,000.

6.25 Assuming that all unassessable and statement only cases are also accurate reports of AAGA gives a 'pessimistic incidence' of ~1 in 12,000 (0.008%).

6.26 The most pessimistic incidence of 'patient reports of suspected AAGA' can be estimated assuming that all 471 original requests for logins were made on some positive grounds, or that the Panel methodology erroneously categorised reports as inadmissible, Unassessable, Unlikely, etc. The overall incidence of patient reports of suspected AAGA is therefore no higher than ~1:6,000 (~0.02%).

6.27 The summary of the different incidences are presented in Table 6.6.

6.28 There is a striking difference between the incidence of AAGA when no NMB is used (~ 1: 135,900) versus when an NMB is used (~1:8,200). The latter figure.

Table 6.6. Estimated 'incidences' for reported AAGA arising out of reports to NAP5. The first column shows the number of reports in that category (n) from NAP5 (Poisson confidence intervals are given in square brackets); the second column shows the number in this category in the Activity Survey from the Activity Survey. *includes all login requests to NAP5 (i.e. an artificially inflated estimate); ** includes all Certain/probable and Possible cases, ICU cases, and cases of drug error

	Activity Survey estimate, n	Incidence	%
Incidence of any report of AAGA made by a patient (n=471)* [429–515]	2,766,600	1: 6,500	0.015
Incidence of AAGA Certain/probable (n = 111) [91–133]	2,766,600	1: 25,000	0.004
Incidence of AAGA Certain/probable or Possible (n = 141) [118–166]	2,766,600	1: 19,600	0.005
Incidence of AAGA when NMB used** (n = 155) [131-181]	1,272,700	1: 8,200	0.012
Incidence of AAGA when no NMB used** (n = 11) [5–19]	1,494,00	1:135,900	0.001
Incidence of AAGA reports after sedation by anaesthetists (n = 20) [12–30]	308,800	1: 15,500	0.006
Incidence of AAGA with Caesarean section (n = 12) [6–20]	8,000	1: 670	0.150
Incidence of AAGA in cardiothoracic anaesthesia (n = 8) [3–15]	68,600	1: 8,600	0.012
Incidence of AAGA in paediatric anaesthesia (n = 8) [3–15]	488,500	1: 61,100	0.002

is very similar to the incidence for cardiothoracic surgery, where NMB use is commonplace, which might explain over-representation of this specialty in AAGA cases. Another subgroup where NMBs are commonly used with notably high incidence is obstetrics (~1:670). The estimate for AAGA in children (where NMB is used less often) is, on the other hand, very low.

DISCUSSION

Incidence

6.29 A striking finding is that, similar to that of the NAP5 Baseline Surveys (Pandit et al., 2013a and b; Jonker et al., 2014b), the overall incidence of patient reports of AAGA is very low, occurring in approximately 1 in 19,000 general anaesthetics. Even the most pessimistic estimate is <1 in 6000. We believe this is important new information for anaesthetists and patients.

6.30 Of note: these figures are several orders of magnitude less common than the incidence consistently ascertained using the Brice interview (ie ~1:20,000 vs ~1:600). If we assume the Brice method to reveal the 'correct' incidence, then it means that for every ~40 patients who experience AAGA (by Brice) just one will make a report (by NAP5). The reasons for this marked disparity need fuller discussion. Methodological differences may be relevant (including inherent weaknesses in the Brice interview, versus weaknesses in the process of NAP5 data collection).

6.31 The differences may also relate to the possible impact the AAGA has had on the patient. The theoretical reasons for not reporting an experience are diametrically opposed: either because it was so trivial that it simply does not warrant a report; or because the event was so traumatic that it is difficult or impossible to make a report. Some support for the first interpretation may lie in the fact that the incidence of distress at the time of the event or psychological sequelae afterwards did not differ between early and late reported cases (see Chapter 7, Patient Experience). Also in studies using the Brice interview, about one-third of patients reporting pain or distress associated with their AAGA experience (Avidan et al., 2008 & 2011) indicating that the majority are neutral events. This is similar to the proportion reporting distress in the NAP5 Baseline Survey (Pandit et al., 2013a & b), but (consistent with the first proposition), lower than the ~50% we now report. Furthermore, Villafranca et al. (2013) describe a patient who responded positively to a Brice interview, but maintained that the experience was so trivial that he did not wish to discuss it further.

6.32 Yet in some support of the second interpretation, our data for Statement Only cases reveals several patients who clearly exhibited forms of phobic avoidance for decades after AAGA (see Chapter 30).

The relative proportions of 'too trivial' versus 'too traumatic' experiences in a 'Brice-positive' cohort are unknown and this warrants formal investigation. Nevertheless, it would appear that the Brice interview in its current form is uncovering a memory that was (as a result of either triviality or trauma) previously inarticulated.

Specific depth of anaesthesia monitoring

6.33 In contrast to the overwhelming prominence of neuromuscular blockade and its (lack of) monitoring, DOA monitors feature little in our results. NAP5 is not a project about DOA monitoring: if for no other reason, this is because DOA monitors are very rarely used as a guide to anaesthesia in the UK. The Activity Survey estimates just 2.8% of all general anaesthetics involve the use of any form of DOA monitoring. This is despite guidance from the National Institute for Health and Care Excellence a full year before the activity survey was conducted, notwithstanding some criticism (Pandit & Cook 2013). The isolated forearm technique (IFT) is even less frequently employed (just ~0.03% of all general anaesthetics (Sury et al., 2014). The use of DOA monitors in Ireland is somewhat higher (~9% of all general anaesthetics) but hardly commonplace (and the IFT is not used) (Jonker et al., 2014a & b). It is unknown if this pattern is mirrored in other countries.

6.34 There was an over-representation of use of depth of anaesthesia monitors in AAGA cases by ~50%, superficially suggesting lack of the benefit from them. However we do not know if they were used appropriately in cases where AAGA occurred. Furthermore, these monitors appeared to be used selectively. The details of DOA monitoring are further explored in Chapter 20.

Inherent resistance to anaesthetic agents

6.35 There was some evidence from our data of differential risk of AAGA with different anaesthetic agents: increased with thiopental and lower for sevoflurane compared with other volatiles. Variation

in the risk of AAGA with different anaesthetic agents and the potential for heterogeneity in coding for protein channels on which anaesthetic agents likely act provides some support for the idea of a genetic role in patients' susceptibility to anaesthetic agents or conversely risk of AAGA.

6.36 In this regard, the NAP5 data contain two potentially relevant results. First, is the finding that within the AAGA reports arising in the maintenance phase of anaesthesia, the causality for 25% was unexplained. Second is the finding that there were six possible cases of previous AAGA and one possible family history of AAGA in our Certain/probable or Possible AAGA reports (i.e. in 5% of cases overall there was some family history). This is not an insignificant proportion. Aranake et al. (2013) have reported that AAGA is up to five times more likely in patients with a previous history of AAGA (an incidence of 1.7%, ~1:60 using Brice questionnaire), which suggests an influence of inherent patient factors. However, NAP5 methodology does not allow us to explore these intriguing speculations further.

Summary

6.37 The detailed analysis of discrete sections of this data (e.g. relating to phases of anaesthesia, subspecialties and monitoring) are discussed in later chapters of this Report.

6.38 The overview of the NAP5 data, especially the data on incidence, make one conclusion compelling. If sustained learning through data collection for a relatively uncommon but important condition is to occur, then an ongoing national database of cases is necessary, modelled on the process used by NAP5.

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