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Abstract

Background. Details of current UK drugs and allergen exposure were needed for interpretation of reports of perioperative anaphylaxis to the Sixth National Audit Project (NAP6).

Methods. We surveyed United Kingdom National Health Service hospitals for this purpose. We also surveyed anaesthetic activity, which is reported separately. Results are compared to a similar 2013 survey for NAP5 where relevant.

Results. From 342 (96%) hospitals we collected 15 942 forms: equating to an annual caseload for anaesthetists of 3 126 067 including 2 394 874 general anaesthetics (GAs). Propofol was the dominant induction agent (90.4%) and used more often in Caesarean section than in NAP5. Nitrous oxide use has fallen 30% since NAP5. Neuromuscular blocking agents were used in 47.2% of GAs. Suxamethonium use has fallen. Use of reversal agents is overall unchanged, but sugammadex use increased 4-fold. Analgesics were used in 88% of cases: opioids 82.1%; paracetamol 56.1% and non-steroidal anti-inflammatory drugs 28.3%. Overall antibiotic use was 57.2% of cases and >3 million annual perioperative administrations: gentamicin 19.7%, co-amoxiclav 17.0% and cefuroxime 13.6% were prominent. In 25% of teicoplanin or vancomycin uses allergy history influenced drug choice. Local anaesthetics were used in 74.2% cases and 68.9% of GAs. Anti-emetics were used in 73.1% of cases: during GA, ondansetron in 78.3% and dexamethasone in 60.4%. Blood products were used in ≈3% of cases, synthetic colloids in <2% (starch in only 1 in 600 cases), tranexamic acid in ≈6%. Chlorhexidine and iodine exposure were reported as 73.5% and 40.0% of cases and a latex-free environment in 21.2%. Exposure to bone cement, blue dyes and x-ray contrast were each reported in 2-3% of cases.

Conclusions. This extensive national survey of anaesthetic practice provides new insights into drug uses and allergen exposures in perioperative care. It is important for use as denominator in the main NAP6 analysis and the data provide significant insights into many aspects of perioperative practice.

Keywords

audit; anaesthesia; allergen exposure; drugs

The Royal College of Anaesthetists National Audit Projects (NAPs) study major complications of anaesthesia and concurrently review current practice and use the findings to improve patient care. The Sixth National Audit Project of the Royal College of Anaesthetists (NAP6), is a large-scale prospective service evaluation of perioperative anaphylaxis across the hospitals of the United Kingdom. It has gathered comprehensive quantitative and qualitative information on these events, enabling the anaesthetic and allergy/immunology communities to collaborate in order to make recommendations for the improvement of the quality of patient care.[1-3]

During the NAP6 project a one-year registry was established to collect reports on all suspected cases of perioperative anaphylaxis in 2015-16. This provided a numerator, but in order to interpret the results of the registry and to estimate the incidence of perioperative anaphylaxis overall and of its causes (drugs/other substances), contemporary information about anaesthetic activity, drug use and exposure to other relevant substances (such as antiseptics and dyes), was required. This data would provide a denominator.

In 2013, the NAP5 project reported a similar activity and drug survey,[4] providing information on aspects of anaesthetic activity and some drug uses, but insufficient for the needs of NAP6. Published Hospital Episode Statistics (HES)[5] show an increase in inpatient and day case procedures since 2013, but do not give detailed information on anaesthetists' involvement. NHS Maternity Statistics show a slight decrease in deliveries in NHS hospitals since 2013, of which 60% involved anaesthetic intervention.[6] Such changes over time mean that figures collected for NAP5 may not necessarily be applicable for NAP6. In addition, the NAP5 survey did not collect sufficient detailed information on perioperative administration of drugs and other potential allergens. National data for hospital drug usage is collected by IQVIA™ and recorded in the Hospital Pharmacy Audit Index (HPAI) database.[7] This records all medication that is issued by pharmacies for use on wards, in operating theatres and on patient discharge. It does not, however, record what is administered to the patient nor in what context a certain drug is delivered, so does not provide information on actual perioperative drug use.

An 'Activity/Allergen survey' was therefore designed to collect such data and this is reported here. During the survey, anaesthetic activity data and drug/allergen exposure data was collected. The 'Activity survey' is reported separately[8] and here we report results of the 'Allergen survey'

Methods

The NAP6 project was defined as a service evaluation by the Health Regulatory Authority therefore did not require National Research Ethics Service approval. All NHS hospitals, Trusts

and Boards in the UK believed to undertake surgery were invited to, and did, volunteer a local co-ordinator (LC) who supervised all aspects of the study at that location.

Local co-ordinators (LCs) were approached at 356 NHS hospitals and organised data collection from every perioperative case involving care delivered by an anaesthetist for a period of 48-hours. This included all adult and paediatric cases requiring general, regional and local anaesthesia, as well as sedation if involving an anaesthetist. Obstetric cases included epidural pain relief in labour. Any cases where sedation or local anaesthesia was delivered by a non-anaesthetist were not included. Routine sedation in intensive care was excluded.

The majority of data collection took place between 13th and 31st October 2016, during which time there were no public holidays; seven sites collected data between January and June 2017 for logistical reasons. Data were recorded using a paper proforma (Appendix 1) and each form was transferred, using optical character recognition, to electronic storage. Each hospital was randomised to record activity on two consecutive days of the week, with specialist hospitals (cardiac, neurology or paediatric centres) block-randomised separately to prevent skewed allocation. Patient characteristics, method of anaesthesia, anaesthetic staffing, induction location, type of monitoring and drugs/substances used, and the presence of any allergy history were reported for each case. Local co-ordinators were also asked to record a capture rate at their site to estimate the proportion of cases for which a completed case report form was submitted. Data regarding staffing, workload and anaesthetic activity are reported separately.[8]

Data were analysed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp. Armonk, New York). An annual caseload was estimated by multiplying the number of cases by a scaling factor. This factor was calculated by converting the number of cases from two days to one week (scaling factor of 3.5), and from one week to one year (scaling factor of 50.6, the effective number of working weeks in 2016 (Appendix 2). This was then divided by the hospital response rate, the mean reported capture rate at individual sites and the proportion of interpretable forms, to account for cases that were not reported. Responses marked as 'unknown' and incomplete fields were combined and reported as 'unknown'.

Here we report data relevant to allergen exposure in the perioperative period and relating to anaesthetist practices in using certain drugs. Where relevant this data is compared to that from the 2013 NAP5 study.[4]

Results

Out of 356 sites approached, 342 took part in the survey submitting a total of 15 942 forms. Applying the calculated scaling factor, the estimated annual caseload was 3 126 067. The distribution of numbers of forms returned from each hospital are shown in Supplementary figure 1. Where relevant, illogical forms (e.g. patients reported to be awake when neuromuscular blocking agents (NMBAs) were used), were excluded but these represented <1.0% of any analysis.

The scaling factor was 196.09. Patient Characteristics are described in the accompanying paper.[8]

Intended conscious level was reported as general anaesthesia (GA) 76.6% (annual estimate 2 394 847) sedation 8.2% (258 250 cases) and awake 14.2% (442 379 cases) (Supplementary table 1).

Anaesthetic Drug Use

Previous Allergy History and Choice of Drugs

Choice of drugs was reported as influenced by previous allergy history in 1 351 cases (8.6% of 15 723 responses); in 64% because of allergy to an antibiotic, 35% allergy to another drug and in 3% to both.

Number of Drugs Used per Procedure

The median number of drugs given in each procedure was 8, minimum 1 and maximum 20 (Supplementary figure 2).

Induction Agents

In terms of allergen exposure: induction agents were used in 13 019 cases including all intended conscious levels: estimated annual caseload was 2 552 896 (Supplementary table 2).

For cases performed with general anaesthesia 15% of returns indicated two induction agents with a volatile reported as an induction agent in 14.8% of cases and a combined volatile/IV induction in 9%: of those with volatile co-induction 51% were adults (Supplementary table 2). As some respondents had likely included both an intravenous and a volatile agent as an 'induction agent' to determine the primary induction agent we only analysed a subset of these cases where one agent was used.

Considering only patients who received general anaesthesia induced with a single agent, or a single agent and midazolam, (n=10 969) the distribution of drugs used was propofol 90.4%, and thiopental 1.6%, ketamine 0.7%, etomidate (0.3%), sevoflurane (6.2%) other volatile agents (0.1%). Midazolam was used as a sole agent in 0.1% of cases (predominantly urgent/emergency cases in ASA 4 - 5 patients) and as a co-induction agent in 7.5%. These proportions did not vary significantly whether midazolam was included or not (Supplementary table 3). These results suggest a small reduction in use of thiopental (1.6% from 2.9%) and an equivalent increase in the use of propofol (90.4% from

88%) since 2013.[4]Cases involving a volatile agent alone for induction were predominantly children (86%).

Propofol was the most widely used induction agent in all groups: 57.7% in children (<16 yrs), 96.2% in adults and 89.7% in patients aged >65 yrs. Distribution of induction agents used by age is shown in Supplementary figure 3). Sixty four patients undergoing Caesarean section, received general anaesthesia; thiopental was used in 62.7% (97% in NAP5), propofol in 29.7%, midazolam and ketamine in 1.6% each. Etomidate and sevoflurane were not used (Supplementary figure 3).

Maintenance Agents

Amongst general anaesthetics where a maintenance agent was used, as inhalational agents was used in 94.6%; sevoflurane in 69.9% (58.5% in NAP5), nitrous oxide in 17.1% and propofol in 8.7%. In 2.2% of cases, both a volatile agent and propofol were used as maintenance agents (Supplementary table 4).

The drug exposure survey showed that 293 (14%) of paediatric cases were administered with sevoflurane only (both for induction and maintenance) with no other agents. Thus a large cohort of children had an extremely low risk technique as far as antigen exposure is concerned.

The use of maintenance agents by age and in Caesarean sections is illustrated in Supplementary figure 4; sevoflurane was the preferred maintenance agent across all age groups and indications. Induction and maintenance exclusively with sevoflurane was reported in 2.8% of general anaesthetics: 14.5% of paediatric and 0.4% of adult general anaesthetics. Sevoflurane was used during general anaesthesia for 90.6% Caesarean sections. Nitrous oxide was reported to be used in 17.1% of cases, 30.1% in children and 60.9% during Caesarean section: a fall from 2013: 25% overall, 45% in children and 71.4% in Caesarean section. Nitrous oxide was used most frequently during general anaesthesia in orthopaedics/trauma, general surgery and ENT, perhaps associated with the increased numbers of paediatric in these specialties.[4]

Neuromuscular Blocking Agents (NMBAs)

NMBAs were reported to be used in 5760 (47.2%) cases receiving GA; estimated annual caseload 1 129 478. Use of NMBAs and estimated annual caseload are detailed in Supplementary table 5. Of those receiving NMBAs, 88.8% received non-depolarising NMBAs only, 4% suxamethonium only and 7.2% both suxamethonium and a non-depolarising NMBA (Supplementary figure 5). Use of different NMBAs in all GA cases is illustrated in Figure 1. Atracurium (23.2%) and rocuronium (19.2%) were the agents most commonly used, followed by suxamethonium (5.3%), with cisatracurium,

mivacurium, vecuronium and pancuronium being used rarely. The distribution of NMBAs was not captured in the NAP5 survey.

(Figure 1 near here)

Within age groups, NMBAs were used in 23% of children, 49.6% of adults and 58.2% of elderly patients, and in almost all general anaesthetic Caesarean sections (98.4%); distribution shown in Figure 2 and Supplementary figure 6. These figures are stable since NAP5.

(Fig 2 near here)

In most specialties atracurium and rocuronium were used predominantly, with the main exceptions being cardiac surgery, obstetrics and psychiatry. In cardiac surgery, pancuronium and vecuronium were used, in 25.7% and 17.9% of cases, respectively. All psychiatry cases received suxamethonium and 1.3% also received atracurium. The distribution of NMBAs in obstetrics was suxamethonium 72.5%, atracurium 35.2% and rocuronium 23.1%; 16.9% received only a non-depolarising NMBA.

Distribution of NMBA use by specialty and by clinical setting is shown in Supplementary figures 6-8. One notable finding is that in ICU, suxamethonium use was absent and rocuronium was used more often (>50%) than in any other location. Conversely in the emergency department, suxamethonium was widely used and rocuronium notably less often (supplementary Figure 9).

When suxamethonium was used, propofol was the induction agent in 73.6% of cases and thiopental in 22.4%, with other agents used rarely. Supplementary figure 10 shows use of induction agents by NMBA. Use of suxamethonium and rocuronium by age and NCEPOD priority is depicted in Supplementary figure 11.

Reversal Drugs

Reversal agents were used in 62.2% of patients undergoing a general anaesthetic with an NMBA. In cases involving a non-depolarising NMBA, reversal was used in 64.6% (68% in NAP5[1]). Neostigmine was used in 59.4% (91.9% of all reversed cases) and sugammadex in 5.9% (9.1% of reversed cases). Sugammadex is now used in almost four-fold more cases than seen in 2013 (2.2% of reversals).[4] Supplementary table 6 details reversal agents used and estimated annual caseloads.

Analgesics

Analgesics were used in 88.2% of all cases (any intended conscious level); estimated annual caseload 2 755 849. Opioids were used in 82.5% of all cases. Paracetamol was administered in 56.1% and a non-steroidal anti-inflammatory drug in 28.3% of cases.

Fentanyl was the most frequently used opioid, administered in 61% of cases, followed by morphine in 26.5% and remifentanil in 8.7% of cases. Diclofenac was the most commonly used NSAID, followed by parecoxib and ibuprofen. Clonidine was administered in 0.9% of cases. Use of each analgesic drug is illustrated in Figure 3 and estimated annual caseload in Supplementary table 6.

(Fig 3 near here)

Opioids were used more frequently during general anaesthesia than in other cases. At least one opioid was used in 99.8% of general anaesthetics: fentanyl in 73.7%; morphine in 33.0%, remifentanil in 10.7%. Paracetamol was used in 67.5%. The distribution of use of different analgesic drugs by intended conscious level is illustrated in Supplementary figure 12.

Antibiotics

Antibiotics were used in 57.2% of all cases, with an estimated annual caseload of 1 787 360. Gentamicin (19.7%), co-amoxiclav (17.0%) and cefuroxime (13.6%) were the three most commonly used antibiotics (Figure 4), with estimated annual caseloads of around a half a million for the former two and approximately 400,000 for the latter. Supplementary table 8 details antibiotics used and estimated annual caseloads.

(Fig 4 near here)

In a quarter of cases where teicoplanin or vancomycin were used (287/1120 and 23/90 cases, respectively), their choice was reported to be influenced by past allergy history to an antibiotic (Supplementary figure 13).

The greatest proportion of all antibiotics use by surgical specialty was in orthopaedics/trauma, accounting for 23.1%, followed by general surgery (14.4%), obstetrics (9.2%), urology (8.9%) and gynaecology (6.5%; Figure 5). The proportion of cases administered antibiotics by specialty was, in descending order cardiac surgery 97.2%; neurosurgery 89.4%; urology 81.7%; thoracic surgery 80.9%; orthopaedics/trauma 69.9% and general surgery 60.3% (Figure 5).

(Fig 5 near here)

Co-amoxiclav was commonly used across most specialties. In ophthalmology, cefuroxime was the most common antibiotic used. In cardiac surgery and cardiology, the dominant antibiotic was gentamicin, with flucloxacillin, cefuroxime and teicoplanin also being frequently used (Figure 6). Use of antibiotics in orthopaedics/trauma was almost evenly spread between gentamicin (32.7% of all orthopaedics/trauma procedures), teicoplanin (21.3%), flucloxacillin (18.2%) and cefuroxime (17.9%, Figure 6).

(Fig 6 near here)

Co-amoxiclav

Co-amoxiclav was the most commonly used antibiotic: 21.6% of all antibiotic uses. It was regularly used in general surgery (27.5% of all cases receiving this drug), gynaecology (15.4%) and obstetrics (13.6%). Choice of co-amoxiclav was not influenced by past allergy history (94.2%).

Teicoplanin

Teicoplanin accounted for 8.9% of all antibiotic administrations. It was used mainly in orthopaedics/trauma (17.5% of all cases receiving this drug), general surgery (16.9%) and gynaecology (10.8%). In 25.6% of cases receiving this antibiotic its choice was determined by previous history of antibiotic allergy.

Local Anaesthetics

Local anaesthetics (LA) administered by any route, were used in 74.2% of all cases and in 68.9% of all general anaesthetics. The proportion of LA drug use was bupivacaine 33.3%; lidocaine 32.0%; levobupivacaine 25.6%; ropivacaine, prilocaine and other LAs each <3% each. Supplementary table 9 details LA use and estimated annual caseloads. Use of LAs by conscious level is detailed in Figure 7.

(Fig 7 near here)

Anti-emetics

Anti-emetics were used in 73.1% of all cases: ondansetron in 65.6% of all cases; dexamethasone in 48.5%; cyclizine in 5.7%; all other anti-emetics <2% (Supplementary table 10 for details of anti-emetic use and estimated annual caseloads). During general anaesthesia, antiemetic use was higher: ondansetron 78.3% of cases and dexamethasone 60.4%. Ondansetron and dexamethasone were used in combination in 53.1% of all GA cases.

IV Colloids and Blood Products

Intravenous colloids and/or blood products were used in 4.2% of all cases. Gelatin-containing products (1.7% of all cases) and red blood cells (1.5%) were the most frequently used products). Starch or starch-containing products (0.2% of all cases), albumin (0.1%), platelets (0.4%), fresh frozen plasma (0.5%) and specific coagulation factors (0.2%), were used uncommonly. Supplementary table 11 details use of IV colloids and blood products and estimated annual caseloads. The surgical specialties that used the greatest proportion of IV colloids or blood products were orthopaedics/ trauma, general surgery, cardiac surgery and obstetrics (1.0%, 0.8% and 0.5% each, of all cases, respectively). The specialties that used IV colloids or blood products most frequently were cardiac surgery, other major operations and vascular surgery (56.6%, 16.7% and 13.6% of cases within each specialty, respectively). Supplementary figure 14 details use of these substances by main procedure. There was no evidence that starch use was concentrated in a particular site or specialty.

Drugs Affecting Coagulation

Drugs affecting coagulation were used in 8.3% of all cases. Tranexamic acid was the most common drug used (5.9% of all cases), followed by heparin (2.7%). Protamine, aprotinin, vitamin K and other coagulation drugs (not specified) were used in less than 1% of all cases. Supplementary table 12 details use of drugs affecting coagulation and estimated annual caseloads. Use of these drugs was mostly concentrated in orthopaedics, cardiac and vascular surgery (52.2%, 25.4% and 10.9% of all cases where a coagulation drug was used, respectively). Tranexamic acid was administered in 71% of cardiac surgery and 19% of orthopaedic operations.

Antiseptics

Use of antiseptics and estimated annual caseload is detailed in Supplementary tables 13 and 14.

Chlorhexidine

Chlorhexidine exposure was reported in 73.5% of all cases, mostly via skin prep by the anaesthetist (51.6% of all cases, accounting for 70.2% of all chlorhexidine-exposed cases) and/or the surgeon (44.7% of all cases, 60.7% of chlorhexidine-exposed cases), with very few cases reported to be via urethral exposure (3.3% of all cases), coated/impregnated CVC, surgical irrigation, or other (0.6% of all cases each for the latter three routes). Exposure to this antiseptic was reported to be unknown in 0.9% of all cases and 23.6% of cases were reported to have no exposure. Chlorhexidine exposure was reported in more than two thirds of cases for most surgical specialties (Supplementary figure 15).

Povidone-iodine

Povidone-iodine exposure was reported in 40.0% of all cases, mostly via skin prep by the surgeon (36.7% of all cases, accounting for 91.7% of all povidone-iodine-exposed cases) or by the anaesthetist (6.6% of all cases, 16.4% of povidone-iodine-exposed cases), with minor contributions by surgical irrigation (0.9% of all cases) or other routes (1.0% of all cases). A total of 54.6% of cases were

reported to have no exposure. Povidone-iodine was used in less than half of cases for all surgical specialties except for ophthalmology, where its use was almost ubiquitous (95.6%), and neurosurgery, vascular, general surgery and plastics, where it was used in more than half of the cases (Supplementary figure 15).

Latex

More than two thirds of cases (69.7%) were reported to be exposed to latex, with the main route being latex gloves (64.3% of all cases, accounting for 92.1% of all latex-exposed cases). A latex-free environment was reported for 21.2% of all cases and latex exposure was unknown for 7.1%. Supplementary table 15 details latex exposure and estimated annual caseload. The specialty with highest rate of latex exposure was cardiac surgery (94.8% of cases) and the lowest was psychiatry (30.8%) (Supplementary figure 16).

Miscellaneous Drugs / Substances

Bone cement was used in 2.6% of all cases and in 11.8% of orthopaedics/trauma cases, with an annual caseload of 78,240.

Blue dyes were used in 2.8% of all cases: patent blue in 2% and methylene blue in 0.9%. Both patent blue and methylene blue dyes were mostly used in general surgery: 29.8% and 35.3% of all cases receiving these dyes, respectively.

X-ray contrast was used in 1.7% of all cases, mostly in urology, radiology and orthopaedics: 24.5%, 22.3%, and 14.2% of all cases receiving X-ray contrast.

Supplementary table 16 details use of the above substances and estimated annual caseload.

Discussion

This survey represents the most recent, comprehensive snapshot of anaesthetic activity and drug use in the United Kingdom. It provides unique detailed insight into drug/substance exposure during anaesthetic activity in the perioperative period. In particular compared to the equivalent Activity survey performed in 2013.[1] it provides considerably greater detail on use of analgesics, antibiotics, local anaesthetics, anti-emetics, intravenous colloids and blood products, as well as providing more information on all drugs assessed in that survey, enabling an examination of trends in practice. This survey also provides information on reported exposure to other substances, such as latex, antiseptics (chlorhexidine and povidone-iodine), radiocontrast media, dyes and bone cement.

As not all drug use was studied in NAP5 we can only comment on changes in choice of induction and maintenance agents, NMBAs and their reversal agents. We observed a substantial increase in the use of propofol for induction of anaesthesia for Caesarean section and a reduction in the use of thiopental. NAP5 identified such surgery as particularly high risk for Accidental Awareness during General Anaesthesia (AAGA) and thiopental was highlighted as a particular contributor to that.[9,10] We also saw a reduction (by about a third) of use of nitrous oxide in all age groups. We are aware that nitrous oxide may have become less popular after the publication of the ENIGMA[11] study and some new hospital builds stopped including piped nitrous oxide to theatres. However the publication of ENIGMA-II has dispelled concerns about the safety of nitrous oxide, including in the elderly population.[12] A recent Canadian publication noted that ENIGMA had reduced use of nitrous oxide amongst anaesthesiologists, but that ENIGMA-II had not led to any recovery in usage.[13] Use of NMBAs has remained stable since the 2013 survey[1], with almost half of patients undergoing general anaesthesia receiving NMBAs and with stable distribution across age groups. Regarding choice of NMBA, use of suxamethonium appears to have declined slightly, both overall (5.3% *vs.* 13% of cases in which an NMBA was used) and during Caesarean section (81% vs. 92%). Use of NMBA reversal agents has not increased overall but the proportion of uses of sugammadex has increased four-fold. With the drug soon to come off patent a further increase might be anticipated. Overall the static nature of NMBA use, the persistent under-use of reversal agents and the underwhelming use of neuromuscular monitoring reported in our accompanying paper[8] indicates no evidence of improvement in practice since increased vigilance in this area was recommended in NAP5[9] and described as mandatory in the AAGBI minimum standards for monitoring document in 2015.[14]

This survey provides comprehensive and, to the best of our knowledge, previously unavailable data on the use of multiple drug classes including analgesics, antibiotics, local anaesthetics, anti-emetics, drugs affecting coagulation, intravenous colloids and blood products. These data will be useful primarily in acting as a denominator for the wider NAP6 project[1,2] but we believe these data also have other uses.

Our data show that analgesics are used in ≈90% of all procedures involving an anaesthetist and that opioids are used in virtually all general anaesthesia cases, a modest increase from NAP5 (92%). With increasing concerns about use of opioids for reasons of both immune function and dependence potential,[15] this knowledge and the distribution of drugs used is useful of itself and for tracking changes. In total an estimated 3.6 million opioid drugs were administered in 3.1 million procedures, with fentanyl and morphine the dominant drugs, and oxycodone (about which some commentators have particular concerns)[16] accounting for <2% of all opioid use and ranking as 5th most frequently used opioid.

The widespread use of local anaesthetics, which were administered in three quarters of all cases, and the distribution of drugs used indicates local and regional anaesthetic techniques were used in three quarters of cases, and with the previous results of NAP5, which indicated neuraxial anaesthesia being used for ≈30% of cases, suggests most suitable cases are receiving neuraxial, peripheral nerve block or local anaesthesia infiltration, the first two of which are associated with improved patient reported satisfaction.[17] These data also provide numerator data – 2.3 million perioperative administration of local anaesthetics – which may be of value when measuring the safety impact of non-Luer connectors on avoidance of wrong route errors.[18,19]

We have documented the use of anti-emetics in approximately three quarters of all cases with dexamethasone now administered routinely (60%) during general anaesthesia. With concerns about the impact of dexamethasone on cancer recurrence[20] and the relatively modest impact of this drug on post-operative nausea and vomiting[21] this is also a notable finding.

Drugs affecting coagulation were used in ≈8% of all cases, with tranexamic acid used in ≈6% of all cases, in the majority of cardiac surgery cases and in one in five orthopaedics/trauma operations. This is likely a relatively new phenomenon, but with tranexamic acid now recommended to be offered to all patients undergoing surgery with anticipated blood loss >500 mls[22] our findings act both as a benchmark, but also suggest that this recommendation may not be being widely applied.

The use of IV colloids, is also of interest in relation both to blood product use (one administration in every 37 cases) and in the use of synthetic colloids (<2% of cases). Amongst the synthetic colloids the gelatins accounted for 90% of use, mostly during cardiac and vascular surgery. Starch-containing fluids are used in approximately 1 in 600 cases and while there was no particular pattern to their use (surgical specialty, patient age, ASA) it did include emergency cases and patients of ASA 3-4. The 26 administrations of starch-containing fluids were reported from only 17 locations suggesting perhaps the use is clustered in certain hospitals. The use of starch containing fluid remains highly controversial and the European Medicines Agency recently recommended their suspension from sale.[23] Based on our data this will have little impact on UK anaesthetic practice.

Amidst the current threat of increasing antibiotic resistance,[24,25] our data provide detailed information on antibiotic usage, which was reported for over half of the procedures and accounted for almost 2 million administrations annually. Gentamicin, co-amoxiclav and cefuroxime being the most commonly used drugs – each used for approximately 500,000 uses. Orthopaedics/trauma and general surgery are the main specialties using antibiotics, but cardiac and neurosurgery, urology and

thoracic surgery are the specialties with the greatest proportion of cases receiving an antibiotic. The wide distribution of antibiotics used within specialties might perhaps hint at a lack of consistent application of best practice, but this would require further investigation.

The choice of drugs administered was reported to be influenced by allergy history in almost 10% of cases and a history of antibiotic allergy influenced choice of teicoplanin or vancomycin in over a quarter of cases when either of these antibiotics were used. We did not collect information on the specific antibiotic(s) that patients reported allergy to, but it is likely that a history of penicillin allergy was dominant, as these drugs are common substitutes for penicillins and penicillin allergy is reported in up to 10% of the general population and 20% of in patients.[26-28] Importantly more than 90% of patients with a history of penicillin allergy are deemed not allergic when investigated via skin and drug provocation tests.[29] The NAP6 baseline survey on anaesthetists' perspectives and experiences of perioperative anaphylaxis reported that penicillins were the drugs anaesthetists were most concerned about and avoided most often. Notably teicoplanin, although prominent among suspected causative agents, was not frequently avoided.[30] There is emerging evidence of teicoplanin as an important trigger of anaphylaxis events[31] and it accounted for 28% of antibiotic-related anaphylaxis in one series.[8] A growing body of evidence has shown that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs with increased duration of treatment and hospital stay, and leads to higher rates of antibiotic resistance and infections including methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* (C. diff) and vancomycin-resistant enterococcus (VRE).[32-34] Our data provide additional evidence of use of second-line antibiotics, namely teicoplanin, driven by drug allergy history, adding further strength to calls from the international allergy community for robust programmes to tackle inaccurate labels of antibiotic allergy, improving antibiotic stewardship.[32-35]

Chlorhexidine is a widely used antiseptic[36] that has been increasingly reported as an emerging cause of allergy and perioperative anaphylaxis in particular,[37-42] although its use still appears to be under-recognised in the healthcare and especially in the perioperative setting and its potential to cause allergic reactions under-estimated by healthcare professionals.[43-45] Despite its known ubiquitous use in the hospital, following infection prevention guidelines, our data evidenced reported chlorhexidine exposure in only ≈75% of all cases, mostly via skin prep by the anaesthetist and/or the surgeon. Very few cases of exposure were reported via urethral exposure and coated/impregnated central venous catheters (CVCs). National guidelines such as NICE CG74[46], recommend use of chlorhexidine to prevent surgical site infections and many local hospital guidelines advocate the use of chlorhexidine prior to venous cannulation. We suspect our data likely reflects under-reporting due to under-recognition of chlorhexidine exposure, for example due to lack of awareness of chlorhexidine being

present in many antiseptic alcohol wipes, urethral lubricants and CVCs. Conversely, it was unsurprising to find that povidone-iodine is used in ≈two fifths of cases and mostly via skin prep by the surgeon.

Finally, our survey data suggest a latex-free environment was in place for only one fifth of cases.

This survey adopted similar methodology to that used for the NAP5 activity survey.[4] Discussion and details on the methodology used, in particular, the duration of the census over two days instead of a longer sampling time, the randomisation of specialist hospitals, and extrapolation of sample data to estimate the annual workload is already considered in the relevant paper.[8] As also noted then, the large size of our sample data set means we can be confident that we have a true representation of the overall anaesthetic activity and allergen exposure in the UK and that it is reasonable to scale-up the 2-day sample data to estimate the annual data. However, where the sample size is small, variations in data captured or missed would have proportionately larger impacts on annual estimates, so these data should be treated more circumspectly.

This survey suggests an annual caseload of 3 126 067, which is a 15% reduction compared to that reported in NAP5 (3 685 800). We are not aware of any comparable data against which to benchmark. Of note, the NAP6 annual estimate of Caesarean section caseload (171 579) is within <2% of that reported in NHS maternity data (174 720).[47] We attempted to control for limitations in data collection by incorporating an estimated capture rate per hospital, accounting for uninterpretable forms, and calculating a scaling factor to include bank holidays. There are many factors that may have contributed to a fall in activity between 2013 and 2016, and these are discussed in the accompanying paper.[8] However, the possibility also exists that we have missed a proportion of cases. If this is the case, we would have underestimated caseload, drug and allergen exposure, and activity by up to 15%. However, it would not impact on relative proportions and patterns of use/exposure within the dataset.

Overall this extensive national survey of anaesthetic practice in the United Kingdom provides new insights into drug uses and allergen exposures in UK perioperative care. It is important for use as denominator in the main NAP6 analysis, and the data provide significant insights into many aspects of perioperative practice.

Declaration of interest

TMC: is an associate editor of the British Journal of Anaesthesia. He is not aware of any financial conflicts.

SM, HK, NH LF, SF, DNL, TG, KFl, HT, MT, AW JH, KFe, WE, SN, SK, K-LK, NMcG and MB all declare they have no conflicts of interest.

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Authors' contributions and authorship

SM - Contributed to design and methodology or the study. Analysed results. Wrote all drafts of the paper and the final draft.

HK – Contributed to design and methodology or the study. Analysed results. Reviewed and revised early drafts of the paper and the final draft

TC - Contributed to design and methodology or the study. Analysed results. Reviewed and revised early drafts of the paper and the final draft.

NH - Contributed to design and methodology or the study. Analysed results. Reviewed and revised early drafts of the paper and the final draft.

LF - Contributed to design and methodology or the study. Administered study. Took part in review of draft manuscript leading to finalisation.

All other panel members contributed to the design and methodology of the study, reviewed the results and took part in review of draft manuscript leading to finalisation.

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Figures

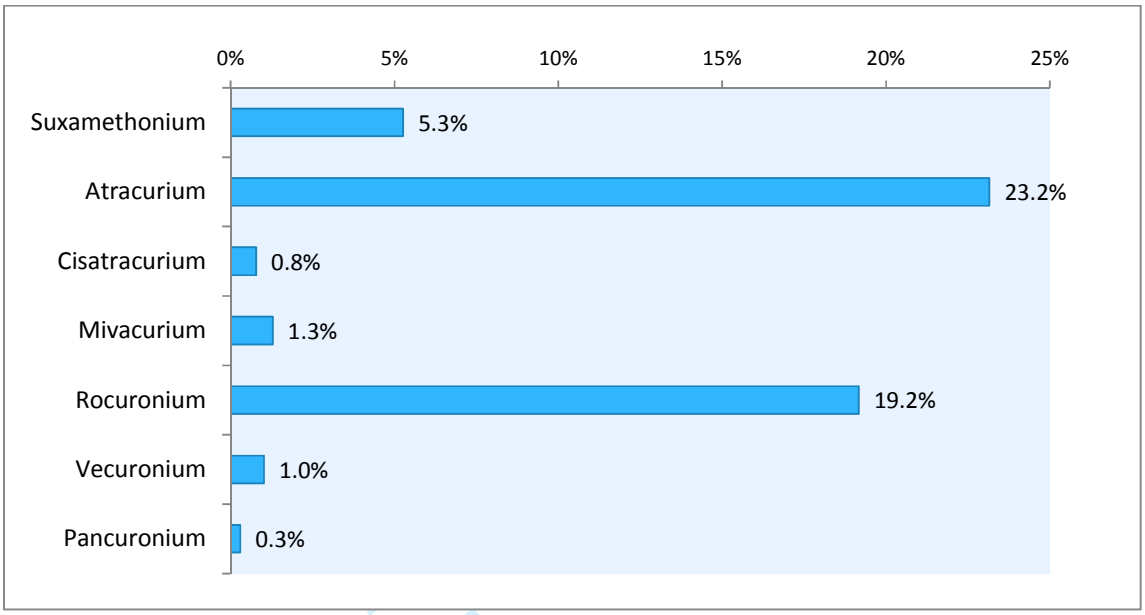

Figure 1 – Use of all NMBA during general anaesthesia (whether individually or multiples), as a proportion of all general anaesthetic cases, N=12,213.

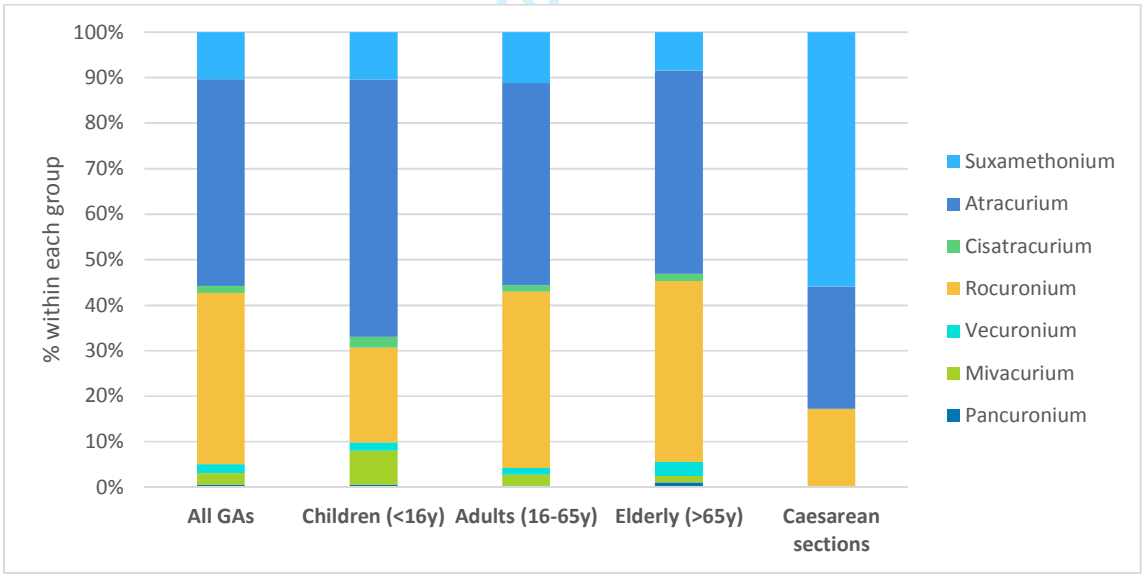

Figure 2 - Use of NMBAs by age group and in Caesarean sections

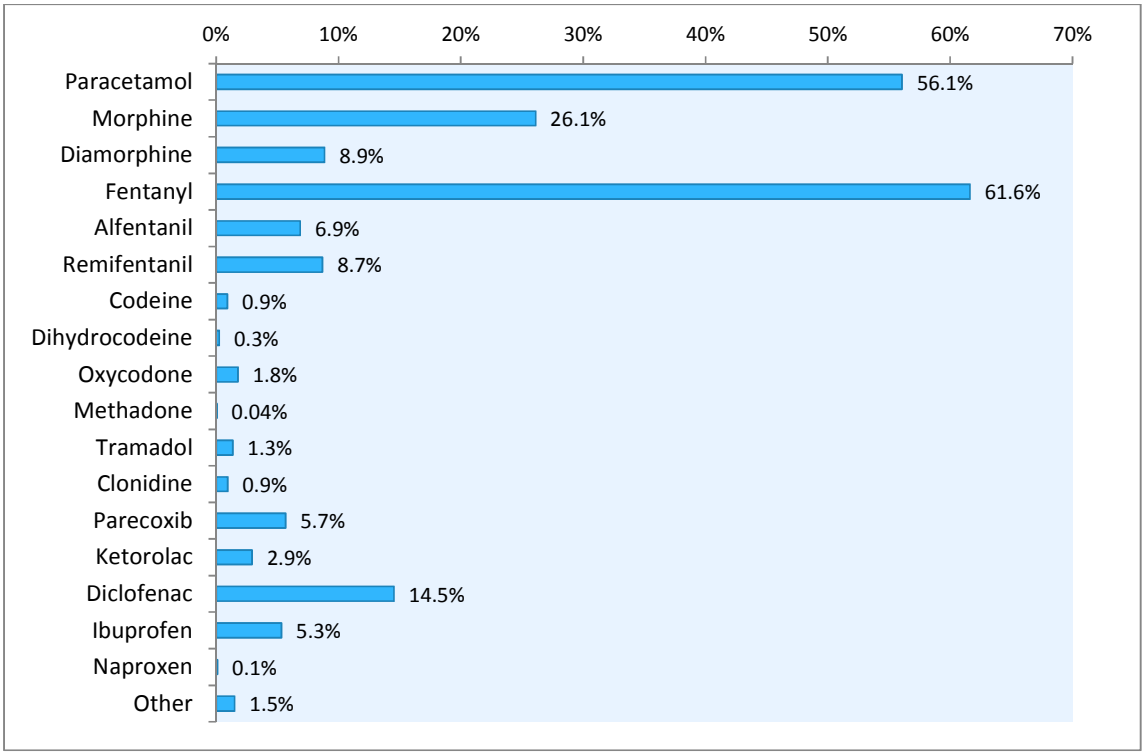

Figure 3 – Use of analgesic agents in all cases

This depicts use of each analgesic drug, whether in isolation or combined, n= 15,776.

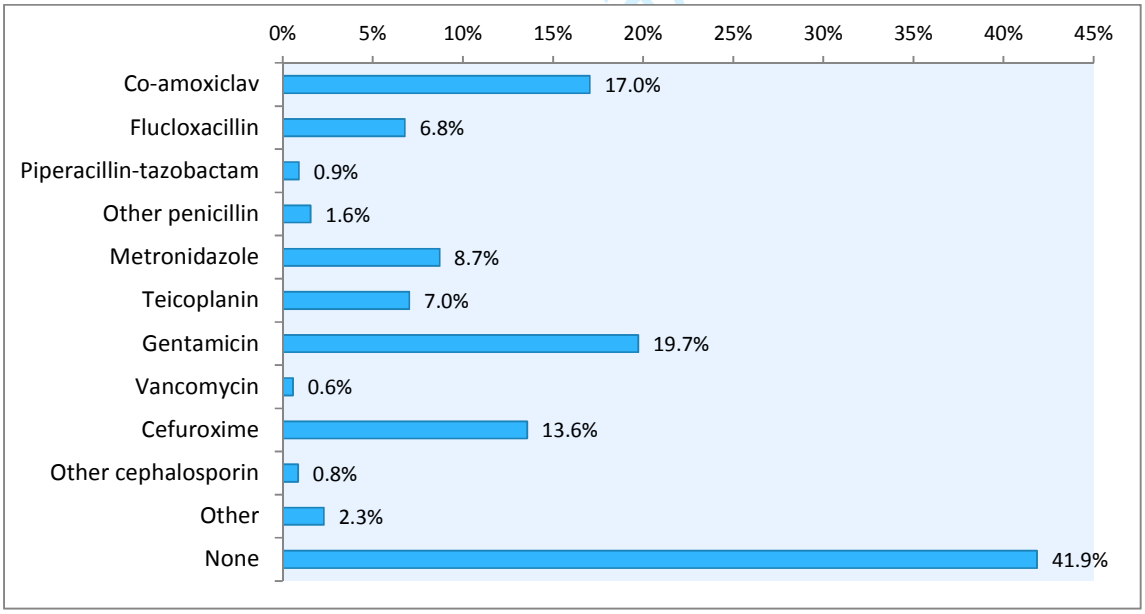

Figure 4 – Use of antibiotics in all procedures.

This depicts use of each antibiotic, whether in isolation or combined, n= 15,790.

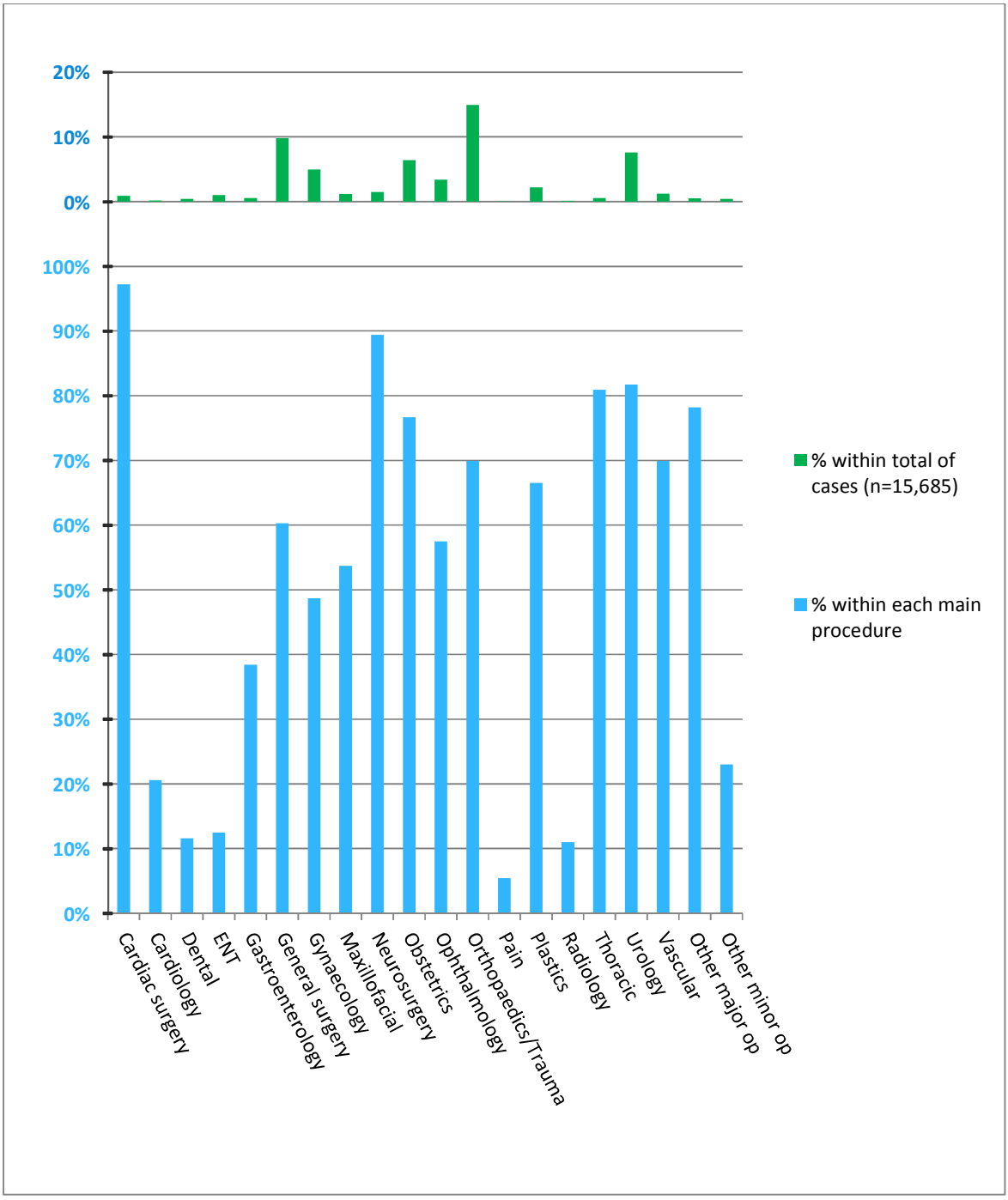

Figure 5 - Antibiotic use by specialty. Top panel indicates the proportion of all cases with antibiotics administered that fell in that surgical specialty. The lower panel indicates the proportion of cases in each surgical specialty receiving antibiotics.

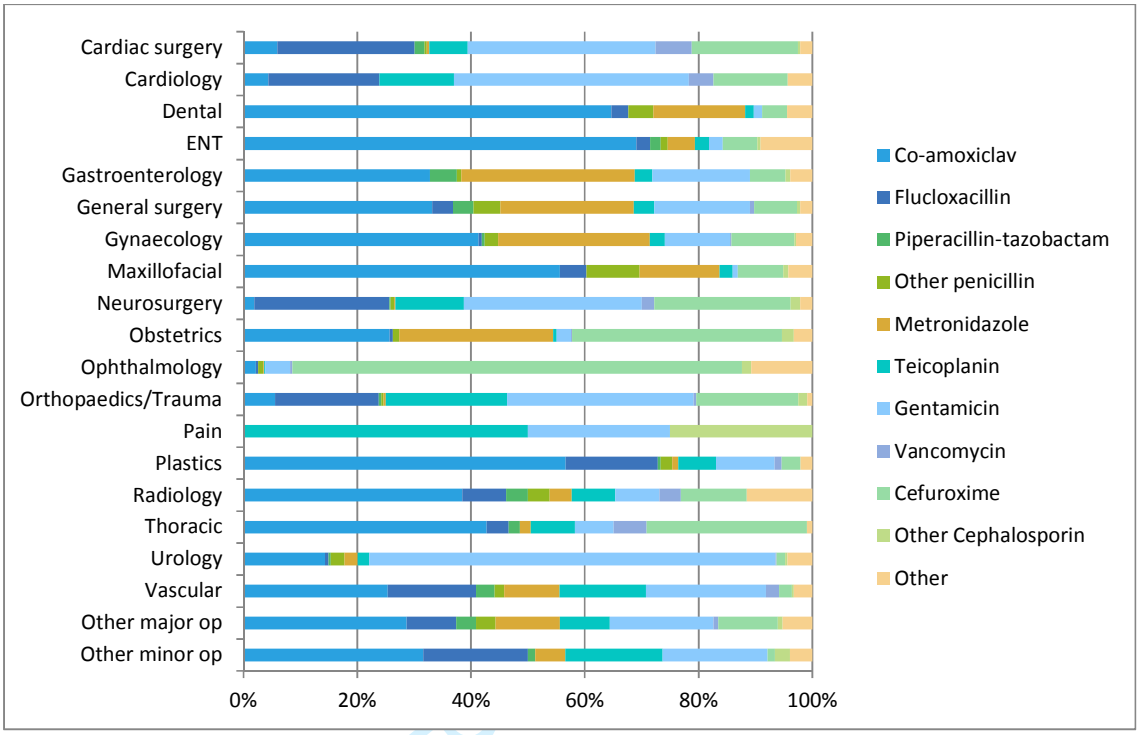

Figure 6 – Distribution of individual antibiotics use by specialty

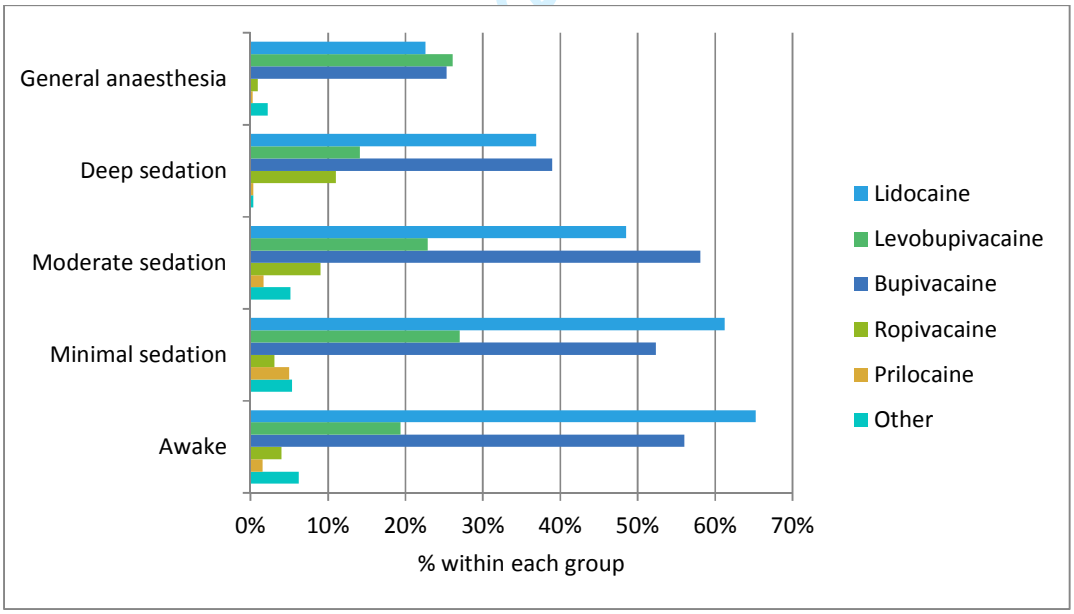

Figure 7 - Use of local anaesthetics by intended conscious level

Appendix 1. Survey questionnaire

NAP6 Anaesthetic Activity/Allergen Exposure Survey

NAP6 Hospital Code: ☐☐☐ Date: d d / m m / y y

PLEASE INDICATE ALL SPECIFIED DRUGS/SUBSTANCES THE PATIENT WAS EXPOSED TO DURING THE PERIOPERATIVE PERIOD (until patient discharged to the ward or HDU/ICU) *PLEASE SELECT ALL BOXES THAT APPLY IN EACH CATEGORY*

Theatre Number/Location: ☐ **Actual List Order** (first patient is 01): ☐☐

Please complete this form for all patients where anaesthesia care is provided by an Anaesthetist during the two day survey period

Day of the Week
☐ Mon ☐ Tues ☐ Wed ☐ Thurs ☐ Fri ☐ Sat ☐ Sun

Admission Type
☐ Elective Day Case
☐ Elective Inpatient
☐ Emergency
☐ Other
☐ Unknown

Main Procedure
☐ Cardiac surgery
☐ Cardiology
☐ Dental
☐ Maxillo-facial
☐ ENT
☐ Gastroenterology
☐ General surgery
☐ Gynaecology
☐ Neurosurgery
☐ Obstetrics
☐ Ophthalmology
☐ Orthopaedics/Trauma
☐ Pain
☐ Plastics
☐ Psychiatry
☐ Radiology
☐ Thoracic
☐ Urology
☐ Vascular
☐ Other minor op
☐ Other major op

Either
NCEPOD Priority
☐ Immediate ☐ Urgent ☐ Expedited ☐ Elective ☐ Unknown

Or
Caesarean Category
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown

Age of Patient (yrs)
☐ <1 ☐ 1-5 ☐ 6-15 ☐ 16-25 ☐ 26-35 ☐ 36-45 ☐ 46-55 ☐ 56-65 ☐ 66-75 ☐ 76-85 ☐ >86 ☐ Unknown

Sex of Patient
☐ Male ☐ Female ☐ Unknown

ASA Grade
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ Unknown

Body Habitus (BMI)
☐ Underweight (<18.5)
☐ Healthy weight (18.5-24.9)
☐ Overweight (25-29.9)
☐ Obese 1 (30-34.9)
☐ Obese 2 (35-39.9)
☐ Obese 3 (>40)
☐ Unknown

Ethnicity
☐ British (White)
☐ Irish (White)
☐ Any other White Background
☐ White and Black Caribbean (Mixed)
☐ White and Black African (Mixed)
☐ White and Asian (Mixed)
☐ Any other Mixed Background
☐ Indian (Asian or Asian British)
☐ Pakistani (Asian or Asian British)
☐ Bangladeshi (Asian or Asian British)
☐ Any Other Asian Background
☐ Caribbean (Black or Black British)
☐ African (Black or Black British)
☐ Any other Black Background
☐ Chinese (Other Ethnic Group)
☐ Any Other Ethnic Group
☐ Not Known

Premed Given on the Ward
☐ Yes ☐ No ☐ Unknown

Induction Location
☐ Theatre anaesthetic room
☐ Theatre
☐ Radiology or Cath-lab
☐ ICU
☐ Emergency Department
☐ Other
☐ Unknown

Intended Conscious Level
☐ General anaesthesia
☐ Deep sedation
☐ Moderate sedation
☐ Minimal sedation
☐ Managed anaesthesia care

Was Your Choice of Drugs Influenced By Previous Allergy History?
☐ No ☐ Yes - antibiotic ☐ Yes - other ☐ Unknown

Latex Exposure During This Case
☐ Yes (gloves)
☐ Yes (other latex)
☐ Latex-free environment
☐ Unknown

Povidone Iodine Exposure During This Case
☐ Skin prep (anaesthetist)
☐ Skin prep (surgeon)
☐ Surgical irrigation
☐ Other
☐ None
☐ Unknown

Chlorhexidine Exposure During This Case
☐ Coated/impregnated CVC
☐ Urethral
☐ Skin prep (anaesthetist)
☐ Skin prep (surgeon)
☐ Surgical irrigation
☐ Other
☐ None
☐ Unknown

Induction Agents
☐ Propofol
☐ Thiopental
☐ Etomidate
☐ Midazolam
☐ Ketamine
☐ Sevoflurane
☐ Other volatile agent
☐ Not applicable
☐ Other
☐ Unknown

Maintenance Agents
☐ Volatile agent
☐ Nitrous oxide
☐ Propofol infusion (not TCI)
☐ Propofol infusion (TCI)
☐ Intermittent bolus Propofol
☐ Other
☐ Unknown

Analgesics (any route)
☐ None
☐ Paracetamol
☐ Morphine
☐ Diamorphine
☐ Fentanyl
☐ Alfentanil
☐ Remifentanil bolus(es)
☐ Remifentanil infusion
☐ Codeine
☐ Dihydrocodeine
☐ Oxycodone
☐ Methadone
☐ Tramadol
☐ Parecoxib
☐ Ketorolac
☐ Diclofenac
☐ Clonidine
☐ Unknown

Neuromuscular Blockers
☐ None
☐ Suxamethonium
☐ Atracurium
☐ Cisatracurium
☐ Mivacurium
☐ Rocuronium
☐ Vecuronium
☐ Pancuronium
☐ Unknown

Reversal Drugs
☐ None
☐ Neostigmine
☐ Sugammadex
☐ Unknown

Local Anaesthetics (any route)
☐ None
☐ Lidocaine
☐ Bupivacaine
☐ Levobupivacaine
☐ Ropivacaine
☐ Prilocaine
☐ Other
☐ Unknown

Antibiotics
☐ None
☐ Co-amoxiclav
☐ Flucloxacillin
☐ Other penicillin
☐ Teicoplanin
☐ Gentamicin
☐ Vancomycin
☐ Cefuroxime
☐ Ceftriaxone
☐ Other Cephalosporin
☐ Other
☐ Unknown

IV Colloids/Blood Products
☐ Gelatin or gelatin-containing
☐ Starch or starch-containing
☐ Albumin
☐ Red cells
☐ Platelets
☐ Fresh Frozen Plasma
☐ Specific coagulation factors
☐ Other
☐ Unknown

Anti-Emetics
☐ None
☐ Ondansetron
☐ Dexamethasone
☐ Cyclizine
☐ Metoclopramide
☐ Droperidol
☐ Other

Coagulation Drugs
☐ Heparin (any)
☐ Tranexamic acid
☐ Aprotinin
☐ Protamine
☐ Other

Miscellaneous Exposure
☐ Patent blue dye
☐ Methylene blue dye
☐ X-Ray contrast

Monitoring
☐ Depth of Anaesthesia
☐ Peripheral nerve stimulator
☐ Quantitative neuromuscular monitoring
☐ Cardiac output

Most Senior Anaesthetist Present
☐ Consultant
☐ Other career grade doctor
☐ ST4-7
☐ ST3/CT3
☐ CT2
☐ CT1
☐ Other (e.g. research fellow)
☐ Unknown

Appendix 1

Appendix 2

Calculation of Scaling Factor

Number of weeks in the year

It is not possible to multiply the weekly caseload by 52 due to Bank Holidays where activity will be reduced. Assuming activity on a Bank Holiday is similar to a weekend day the 'effective' number of weeks can be calculated. For 2016 the number of weeks used as a scaling factor to estimate annual activity was 50.74:

There were 366 days in 2016 (leap year), and 52.28 weeks (366/7 = 52.29).

Using the number of weekdays, a scaling a factor x, and y as the number of 'effective' weeks in 2016:

5/7 * x = 52.29 and 253/366 * x = y

Therefore x = 7*52.29/5 = y*366/253

And y = (7*52.28*253) / (5 * 366) = 50.6

Multiplication factor

Number of returns in a week = number of returned forms *3.5

Number of returns in a year (2016) = returned forms *3.5 * 50.6

Estimated annual caseload = (returned forms * 3.5 * 50.6) / (proportion of interpretable forms * proportion of hospitals responding * individual site capture rate

Multiplication factor = (3.5 * 50.6) / (0.98*0.96*0.96) = 196.09