

EDITORIAL

Perioperative anaphylaxis — Time for a NAP... 6!

Perioperative anaphylaxis is a severe, life-threatening, generalised hypersensitivity reaction. Although a rare event, it is one of the most hazardous emergencies encountered in the perioperative setting. For those who survive, consequences include abandoned procedures, delay/reluctance in rescheduling, sometimes urgent, procedures until the cause of the reaction is clarified, and associated physical and psychological sequelae with extended hospital stays.

The 6th National Audit Project of the Royal College of Anaesthetists (NAP6) was the largest ever prospective study of anaphylaxis related to anaesthesia and surgery. It studied every case of life-threatening anaphylaxis in over 3-million anaesthetics given in all NHS hospitals in the UK over a 12-month reporting period and incorporated contemporaneous real-life data on exposure to potential allergens, allowing calculation of accurate relative incidence rates. This editorial will focus on some key/novel findings from NAP6,¹⁻³ and what they could mean for future patient care.

From a detailed review of 266 cases (out of 541 reported), the incidence of life-threatening perioperative anaphylaxis (grades 3-5) was estimated to be 1/10 000 anaesthetics; however, due to incomplete data, the true incidence may be higher at ~1/7000 cases.¹ This is similar to that reported in most other studies, though these included perioperative anaphylaxis of all grades.⁴

The incidence of perioperative anaphylaxis appears to be rising, which may be driven by heightened awareness of anaesthetists (something to which NAP6 is likely to have made a major contribution in the UK), but also from changes in perioperative drug use, in particular antibiotics, which are usually co-administered at induction. NAP6 identified that antibiotics are used in 57% of all anaesthetic procedures (~2.5-million annual perioperative administrations) with gentamicin, co-amoxiclav, and cefuroxime being the most common choices and accounting for ~1.5-million exposures.² Although neuromuscular blocking agents (NMBAs) have been reported as the major cause of perioperative anaphylaxis in several countries, such as the United Kingdom⁵ and France,⁴ the French series demonstrated a substantial rise of antibiotics as a cause of perioperative anaphylaxis,⁴ and these are the main culprits in the United States and Spain.⁴ One of the key novel findings from NAP6 was the identification of antibiotics as the leading culprit in the United Kingdom, responsible for almost half of all cases of confirmed perioperative anaphylaxis (of 192 with identified culprits), with an incidence of 4/100 000 administrations.¹ The majority were caused by teicoplanin (16.4/100 000 exposures) and co-amoxiclav (8.7/100 000 exposures), which together accounted for 89% of antibiotic-induced perioperative anaphylaxis. Use of teicoplanin has markedly increased over the last few years and there are some reports of life-threatening reactions to this drug;⁶ nevertheless, it only accounted for ~200 000

annual exposures,² so it is striking that its relative risk of perioperative anaphylaxis was twice that of co-amoxiclav and 17.4-fold higher than that of cefuroxime or flucloxacillin, highlighting teicoplanin as an important emerging allergen. In contrast, and despite its considerable use, the relative risk of gentamicin, when using the same two β -lactams as an index, was only 0.5.

Another notable finding from NAP6, identified in the allergen survey² and on case review,¹ was that a vast proportion of teicoplanin use was driven by patient-reported history of penicillin allergy: more than half of the patients with teicoplanin perioperative anaphylaxis had reported such history preoperatively, and it is likely that in many, penicillin would have been the first-line antibiotic choice; moreover, in at least three cases, the penicillin allergy label was subsequently removed after allergy clinic investigations. Penicillin allergy is reported in ~10% of the population and ~20% of inpatients, but at least 90% could be delabelled if an adequate description of the reaction was available or the patients were investigated in an allergy clinic.⁷ It is currently untenable to investigate all putative penicillin allergy in allergy clinics, even preoperatively, owing to the large numbers of patients affected, the process being complex, and the striking unmet need for allergists/immunologists across the country.⁸ With the importance of antibiotic stewardship amongst the current threat of increasing antibiotic resistance and growing evidence that use of the second-line (often more expensive) antibiotics has significant patient and public health implications and increased healthcare costs,⁷ the NAP6 findings reinforce the need for efficient programmes to remove spurious penicillin allergy labels—including better documentation of reactions, strategies to assess and stratify patient risk, simplify allergy investigations, and safely delabel where appropriate.⁷ The NAP6 allergen survey also identified a wide distribution of antibiotics used within specialties, which might hint at a lack of consistent application of best practice.² Avoiding unnecessary antibiotic administration is one way of reducing the incidence of perioperative anaphylaxis and antibiotic administration should adhere strictly to national/local guidelines on prophylaxis of surgical site infections. There is already work underway to review and harmonise these in some NHS hospitals and we hope this is considered across the country.

Another notable NAP6 finding was that almost all antibiotics were administered after induction of anaesthesia, with signs of anaphylaxis identified in <10 minutes for almost all cases—the most common clinical feature was hypotension.¹ The NAP6 recommendation to administer antibiotics, where practical, 5-10 minutes before induction of anaesthesia should be widely adopted. This is likely to improve detection of anaphylaxis if caused by antibiotics, may simplify treatment, and will greatly simplify allergy investigations if reactions occur (a median of 8 and up to 20 drugs are given per

procedure,² making investigations quite complex when all are given almost simultaneously before a reaction).

NMBAs were the second most common culprit of perioperative anaphylaxis, accounting for ~1/3 of cases. Suxamethonium carries ~twice the risk as that of all other NMBAs (11.1 vs. 3.25–5.88/100 000 exposures).¹ Therefore, concerns about allergy should not be a deciding factor in the choice of NMBA, except in cases of known or strongly suspected allergy, and despite perceptions by 1/3 of anaesthetists of higher risk with suxamethonium and rocuronium, avoiding them for this reason.⁹

Chlorhexidine use varies between countries, but it is an almost ubiquitous antiseptic in the UK healthcare setting, widely used for topical skin disinfection, surgical irrigation, and contained in some lubricating gels and coated CVCs; national (NICE-GC74) and local guidelines advocate its use for prevention of surgical site infections and prior to cannulation. It is a reported emerging cause of allergy and particularly of perioperative anaphylaxis.¹⁰ Nevertheless, its use is underrecognised—exposure was only reported in 73.5% of perioperative cases in the NAP6 allergen survey,² and its potential to cause allergic reactions underestimated—although it was the third most common cause of perioperative-anaphylaxis (9% of all cases), it was only suspected in ~1/4 of confirmed cases (including some where chlorhexidine-coated CVCs were not removed during anaphylaxis);¹ furthermore, two patients with confirmed chlorhexidine allergy were re-exposed, with subsequent anaphylactic reactions. These findings call for action regarding clear labelling of chlorhexidine-containing products/devices (the MHRA issued a warning on this in 2012) and for hospitals to have a chlorhexidine allergy policy—highlighting the need for inclusion of chlorhexidine in the allergy history taken by healthcare professionals, making them aware of sources of chlorhexidine exposure (including ‘hidden’: lubricating gels, coated CVCs), and suggesting alternatives for patients with suspected/confirmed allergy. Although a superior antiseptic to other available alternatives, justifying its ubiquitous use, guidance/policies should consider a reduction in unnecessary exposures to chlorhexidine, for instance in urethral catheterisation in adults. Anaphylaxis to chlorhexidine was often delayed, but more rapid and severe when caused by coated CVCs compared to surgical site exposure.¹ Testing for chlorhexidine was frequently omitted in allergy clinics.³ This should be done routinely when investigating perioperative anaphylaxis—another key recommendation from NAP6, including more than one test modality (skin prick and intradermal tests, serum-specific IgE, BAT) because a single test may be insufficient to exclude allergy. Additionally, in cases of chlorhexidine allergy, tests for other possible drug culprits may also be positive, suggesting that multiple sensitisations may be at play; thus, all relevant exposures should be investigated even when chlorhexidine allergy is confirmed.

Patent Blue dye was the fourth most common cause (4.5% of NAP6 cases), with an incidence of 14.6/100 000 administrations.¹ Reactions were frequently delayed 30–60 minutes and suspected in most cases, although this assumption led to failure to refer or poor investigations in several cases.¹ It is an approved food dye in the United Kingdom (E131) and in the healthcare setting is mostly used for sentinel lymph node biopsy in breast cancer surgery, markedly

improving their detection, which would justify its use despite its relatively high risk of anaphylaxis (NAP6 recommended this to be discussed as part of the consent process).

NAP6 had no reports of latex- or local anaesthetic-induced anaphylaxis,¹ confirming the downward trend of latex allergy and the paucity of reactions to the latter drugs.

The NAP6 survey of anaesthetists’ perceptions⁹ indicated that they can expect to see a case of perioperative anaphylaxis every 7.25 years of practice, in keeping with the later estimated incidence of these events. Being rare, unexpected and sudden, hampers their prompt identification, which is crucial to a successful outcome. The diagnosis is clinical and not always obvious because clinical manifestations are non-specific and may have multiple non-allergic, and more frequent, causes. Hypotension was the most common presenting feature in NAP6 and universal during the episode, whereas bronchospasm was a less common presenting feature, apart from cases caused by suxamethonium, and was present in ~half of all episodes. Skin manifestations were uncommon presenting features and only present in 56% of cases, presumably due to poor skin perfusion.¹ Cardiac arrest and the 10 fatal reactions reported were more common in patients on ACE inhibitors, and fatalities were also linked to treatment with β -blockers, coronary artery disease, older age, higher ASA physical status, and obesity.

NAP6 has proved to be an invaluable project, born out of close collaboration between anaesthetists and allergists/immunologists, identifying novel aspects of perioperative anaphylaxis and producing a wealth of resources and recommendations (<https://www.nationalauditprojects.org.uk/NAP6-Resources#pt>) that is hoped will lead to preventing avoidable anaphylaxis and improved patient quality of care. The NAP6 will be the focus of the President’s Plenary at the 2018 British Society of Allergy and Clinical Immunology Annual Meeting.

ORCID

Susana Marinho  <http://orcid.org/0000-0003-3069-6187>

Susana Marinho^{1,2} 

¹Allergy Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK

²Division of Infection, Immunity and Respiratory Medicine, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK

Correspondence

Susana Marinho, Allergy Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK.
Email: susana.marinho@manchester.ac.uk

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