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EDITORIAL

Perioperative anaphylaxis – what's the risk?

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Capturing data about rare, hazardous events in perioperative care is challenging. The United Kingdom's National Audit Project (NAP) programme, commissioned by the Royal College of Anaesthetists, endeavours to provide practical information for clinicians by systematically examining a large series of such events.[1] Each NAP has focused on a different topic, and most recently the Sixth National Audit Project, 'NAP6', investigated life-threatening perioperative allergic reactions.[2] A review of the methodology and findings of previous NAPs has previously been published in this journal.[3,4]

Prior to NAP6, previous reports from Europe, Australia, the United Kingdom (UK) and the United States suggested an incidence of perioperative anaphylaxis between 1:6 000 and 1:20 000 depending on the definition of perioperative and the severity of reactions included.[5–7] Most of these studies were retrospective and had collected data over several years, complicating interpretation, as the incidence of anaphylaxis to specific culprits is known to vary over time and geographically.[8,9] While some may therefore question the relevance of NAP6 to South African practice, we believe that there are more universal themes and lessons to be gleaned from the project of relevance to South African anaesthesiologists.

Amongst the aims of NAP6 was to estimate the incidence of perioperative anaphylaxis (in the UK), identify the most likely culprits, examine how well anaesthetists manage anaphylaxis and to describe how patients were referred to and investigated by allergy clinics. NAP6 included only cases of 'life-threatening' hypersensitivity (i.e. true anaphylaxis) (grades 3–5) – cases where the reaction included hypotension or bronchospasm, considered a clear threat to life without intervention.

The project involved several phases[10]: baseline surveys to identify anaesthetic perceptions towards culprit agents and current practice in both the perioperative[11] and allergy clinic settings[12]; a snapshot activity survey to measure the number and type of cases involving anaesthetic care annually in the UK,[13] including the annual number of exposures to potential culprit agents,[14] and finally a year-long registry of all cases of suspected perioperative anaphylaxis throughout the UK.[10] The activity survey created a picture of current anaesthetic practices and provided robust 'denominator data' for the project. In the registry phase, cases were reported to the NAP6 team by Local Co-ordinators working in each NHS Trust throughout the UK, providing a numerator and enabling accurate incidences to be calculated. For each case, patient characteristics, type of procedure, agents administered, and immediate management were recorded. Once the patient had been investigated in an allergy clinic, the type of testing, immunological confirmation of the type of reaction and culprit agents identified were recorded. Details of each case were then scrutinised by the NAP6 Steering Committee, comprising anaesthetists, allergists, clinical immunologists and lay members, to confirm the diagnosis, identify the culprit, where possible, and qualitatively assess patient management, immunological investigation, incident reporting and patient harm.

The activity survey estimated around 3.2 million cases were cared for by anaesthetists in the UK in 2017. In all, 541 cases of perioperative anaphylaxis were reported in that year, with only 266 being fully interpretable and meeting inclusion criteria. The overall incidence of perioperative anaphylaxis was estimated at 1:11 752 (95% confidence interval 1:10 422–1:13 303) cases of anaesthesia. This is higher than some previous reports, particularly when it is noted that only grade 3–5 reactions were included. If the cases with incomplete data were also included, the incidence would rise to approximately 1:7 000.

The majority of reactions (81%) occurred after induction of anaesthesia but before surgery. Hypotension was a universal feature and was the first sign in 46% of cases. Bronchospasm was present in > 50% of cases and was the presenting feature in 18%. Notably it was a prominent feature in asthmatic and obese patients. In contrast, airway problems were vanishingly rare and cutaneous signs, if present, occurred late in the time course of the reaction. Indeed, the more severe the anaphylaxis the less common were urticaria, rash and airway swelling. Forty cases (15%) resulted in cardiac arrest, mainly presenting as pulseless electrical activity and/or bradycardia. Tachyarrhythmias and complications of adrenaline administration were virtually absent. Resuscitation from cardiac arrest was successful in 78% but some developed sequelae including longer term cardiac, renal and psychological harm.

Despite profound hypotension being a universal feature of perioperative anaphylaxis, there was inconsistency as to when cardiac compressions were initiated. After consultation, the NAP6 panel agreed that a systolic blood pressure < 50 mmHg should

trigger the initiation of cardiac compressions. We observed that cardiac compressions were omitted in the vast majority of cases of profound hypotension unless the patient was deemed to have developed 'cardiac arrest'. The recommendation to start CPR when the systolic blood pressure is < 50 mmHg although controversial, is reasonable as at this pressure patients will be in a 'pulseless state'.[15]

Ten cases were fatal, an incidence of 1:266 cases of perioperative anaphylaxis and 1:313 000 anaesthetics. Features associated with mortality from anaphylaxis were older age, a higher ASA grade, obesity (90%), pre-existing ischaemic heart disease (50%) and preoperative use of beta-blockers (60%) and/or ACE inhibitors (60%). All fatalities occurred despite prolonged resuscitation attempts.

Anaesthetists were quick to diagnose and treat anaphylaxis. However, in 20% of cases, either adrenaline was not given, or its administration was delayed. Steroids and anti-histamines were administered frequently and (in contrast to concerns raised in Australasian practice) there was no evidence that the administration of antihistamines worsened hypotension or outcomes. The majority of patients received fluids within the first hour, but fluid administration was often judged insufficient: less than the recommended initial bolus of 20 ml/kg, in 19%. Glucagon and vasopressin were rarely used. Since poorer outcomes were associated with beta-blocker and ACE inhibitor use, NAP6 recommended that glucagon (in beta-blocked patients) and vasopressin should be readily available for treatment of any drug-resistant hypotension. More than half of all patients required a catecholamine infusion. In the majority of cases, surgery was abandoned and the patient was transferred to an intensive care unit following stabilisation. Once there, recovery was usually prompt with a median length of stay of one day, and no episodes of recrudescence of anaphylaxis.

The most common culprits identified were antibiotics (47% of cases), a novel finding, as previously neuromuscular blocking agents (NMBAs), here accounting for 33% of reactions, were most frequently identified as the major culprits.[7,16] Other culprits included chlorhexidine (9%), patent blue dye (4.5%) and gelatin-based colloids (1.1%).

Perioperative antibiotic use is highly prevalent in the UK, with over 2.5 million administrations annually and antibiotics administered in over half of all operations. Perioperative anaphylaxis to antibiotics occurred in 1:26 845 uses. Whilst penicillins were perceived by anaesthetists to be the antibiotics with the highest risk of triggering anaphylaxis,[11] the highest risk drug was teicoplanin (16.4/100 000 uses), followed by co-amoxiclav (8.7/100 000 uses) with risk from all other antibiotics being considerably lower. Co-amoxiclav and teicoplanin accounted for almost 90% of all antibiotic-induced anaphylaxis. In 56% of cases where the culprit was identified as teicoplanin, the patient had reported a preoperative allergy to penicillins. In the UK, around 10% of the population report some type of allergy to penicillin[17] and therefore are likely to receive second-line antibiotic therapy.

There is increasing evidence that the use of second-line antibiotics results in other poorer outcomes such as reduced efficacy, increased hospital stay and increased risk of resistance.[18,19] It is estimated that up to 90% of those reporting penicillin allergy are not truly allergic and could be 'de-labelled' by further investigation,[20] thus potentially preventing unnecessary exposure to second line agents, such as teicoplanin. Anaesthetists, as perioperative physicians, could usefully take greater interest in prophylactic antibiotic use. There is potential for us to have an important role in antibiotic allergy de-labelling and we should work with microbiologists and surgeons to explore whether frequency of antibiotic prophylaxis and choice of drugs can be optimised. There is much work to be done here.

The fast onset of reactions to antibiotics identified (over three-quarters within five minutes, and 93% within 10 minutes of administration) lends weight to the argument for delivering antibiotics prior to induction of anaesthesia, to prevent any additive effect of peri-induction and anaphylaxis-related hypotension. If only one or two drugs have been administered before anaphylaxis occurs this also dramatically simplifies investigation of anaphylaxis and identification of the culprit.

The frequent use of 'test doses' prior to antibiotic administration was highlighted in the baseline survey, with 31% of anaesthetists reporting this practice.[11] In 18 cases of antibiotic-induced anaphylaxis a test dose was administered, in 10 of which the reaction occurred after only the test dose was given. The severity of reaction in these cases was no less severe than cases where a test dose was not administered. During allergy testing, typically one thousandth of the full dose is administered, whereas in NAP6 test doses were 5–30% of the full dose. NAP6 reiterated previous advice[21] that antibiotic test doses are of no value in limiting or preventing anaphylactic reactions perioperatively.

In our baseline survey, anaesthetists perceived NMBAs as very high risk of anaphylaxis: 67% reported avoidance of their use due to concerns relating to anaphylaxis and rocuronium and suxamethonium were prominent in these concerns.[4] It is likely that the pattern of NMBA use has changed in the UK in recent years due to the introduction of sugammadex and the opportunity to avoid suxamethonium during rapid sequence induction. Indeed the allergen survey showed a four-fold increase in the use of sugammadex since 2013.[14,22] NMBAs were used in 47% of general anaesthetic cases and atracurium and rocuronium were the favoured agents. However, the incidence of anaphylaxis to rocuronium and atracurium was notably similar (5.88 versus 4.15 per 100 000 uses). The use of suxamethonium is declining (approximately 10% of all NMBA uses) but it accounted for more than 20% of cases of anaphylaxis to NMBAs and its incidence of anaphylaxis (11.1 per 100 000 uses) was twice that of any other NMBA. When anaphylaxis to suxamethonium occurred, it was no more severe than anaphylaxis to other NMBAs but bronchospasm was notably more common. Beyond

these three NMBAs, UK use of other agents is too infrequent to draw any useful conclusions.

There was a single case of confirmed anaphylaxis to sugammadex and the reaction was identified in recovery, about 15 minutes after administration. Sugammadex has been suggested as a therapeutic agent in both rocuronium and non-rocuronium induced anaphylaxis.[23,24] There were 19 cases (7%) where sugammadex was potentially used for this purpose (in nine, rocuronium was suspected as the trigger agent) but there was no evidence of a treatment effect in these cases and overall NAP6 found no evidence to support the use of sugammadex for management of anaphylaxis whatever the suspected trigger.

The full NAP6 report details national, institutional and individual recommendations for how to improve the patient experience of anaphylaxis, not only during the acute event, but also during the investigation of potential culprit agents. The NAP6 report included numerous resources including a 'toolkit' of proformas to help clinicians communicate effectively with both the patient and other healthcare professionals after an episode of anaphylaxis.[2] All these resources are freely available at https://www.niaa.org.uk/NAP6Report and the site also contains links to the report and to lectures and presentations.

Perioperative anaphylaxis is a truly unexpected, life-threatening event that every anaesthetist might expect to come across in their career. The quantitative data from NAP6 should provide anaesthetists with insight into the problem, enable all clinicians (whichever country they work in) to make safe choices in their practice and provide realistic information to their patients. The qualitative analyses and freely available resources should enable effective preparation for these events and reliable management when they occur.

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