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Introduction



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In this introduction we aim to describe why NAP6, the 6th National Audit Project of the Royal College of Anaesthetists (RCOA), was undertaken, and to point towards ways in which we hope this report will enhance quality of care and improve patient experience. We guide you briefly through the various chapters and hope to whet your appetite to read on at least the next chapter (Key Findings and Recommendations) and perhaps even the entire report.

The process of learning starts with listening, and in Chapter 3 a survivor of perioperative anaphylaxis describes her experience, the shock of unexpected events, and aspects of her care.

This theme is continued in Chapter 4, in which lay members of the NAP6 panel set out a patient-centred response to the findings of this report and make recommendations for improving the patient experience.

More than three million anaesthetics are delivered to patients in NHS hospitals each year and, thankfully, the vast majority are uneventful. Minor, expected effects of anaesthesia on cardiovascular and respiratory function are easily recognised and can be treated promptly and effectively.

Occasionally much more dramatic changes in vital signs are seen, and, in extreme cases, the episode presents as a critical event. There are several well-recognised causes of such episodes during anaesthesia, for example, surgical haemorrhage, acute asthma, an acute coronary event, collapse of a lung, or embolism of a blood clot. The preoperative health status of the patient, such as asthma or coronary artery disease, often points to the cause. This information facilitates prompt diagnosis and enables the anaesthetist to target immediate management.

In contrast, perioperative anaphylaxis is a completely unexpected critical event presenting suddenly and without warning, and may occur in patients with no chronic health problems. In severe cases, extremely low blood pressure, impaired circulation, and difficult ventilation of the lungs combine to starve the tissues of oxygen, and shock ensues. In extreme cases, there is rapid progression to cardiopulmonary arrest, which may be fatal despite prolonged attempts to resuscitate the patient. Clinical features during the episode of more than 250 cases of life-threatening perioperative anaphylaxis are presented and discussed in Chapter 10.

It is not surprising that it may take a few minutes for the anaesthetist to exclude other, more common, causes before the diagnosis of anaphylaxis becomes evident and specific treatment is started. We have made allowance for this sequence of events when assessing the promptness of treatment and the quality of immediate management in the cases reported to NAP6.

What is anaphylaxis?

The accepted definition of anaphylaxis is “a severe life-threatening generalised or systemic hypersensitivity reaction” (Johansson 2001). ‘Hypersensitivity’ is an umbrella term describing reproducible symptoms that occur in response to a defined stimulus, such as a wasp sting or a particular food or drug, in a quantity that is tolerated by most people. Hypersensitivity, and therefore anaphylaxis, is usually allergic but this is not always the case, for example, in some reactions to non-steroidal anti-inflammatory drugs.

The severity-grading of hypersensitivity reactions depends on signs and symptoms. Minor or moderate reactions (Grade 1 and Grade 2) are correctly termed ‘hypersensitivity’, and should not be called ‘anaphylaxis’ as only Grade 3, 4 and 5 hypersensitivity can correctly be termed anaphylaxis. Grade 1 is characterised by cutaneous features such as rash, itch or peripheral swelling; Grade 2 by mild hypotension or wheeze (usually not requiring treatment), with or without Grade 1 features. In Grade 3, these features are severe, and may include airway swelling. Grade 4 fulfils the requirements for initiating cardiopulmonary resuscitation, and Grade 5 is a fatal reaction. We considered including Grade 1 and Grade 2 hypersensitivity in NAP6, but concluded at an early stage that the increased number of reports would be unmanageable. In addition, we felt that learning opportunities were more likely to occur in cases of life-threatening perioperative hypersensitivity.

The majority of anaphylactic reactions occur in the community, but more than a third of all patients admitted to intensive care with severe anaphylaxis come from operating theatres (Gibbson 2012). In relation to anaesthesia, anaphylaxis can occur in the preoperative ward in response to premedication drugs, in the operating theatre, and in the recovery room. The term ‘perioperative’ in relation to NAP6 includes all these sites, as well as interventions requiring anaesthesia care in critical care units, emergency departments, and anywhere else in the hospital that anaesthetist-delivered care is provided.

What triggers anaphylaxis during anaesthesia and surgery?

Patients are exposed to a large number of potential trigger agents during surgery and other invasive procedures. An average of eight drugs are administered during a general anaesthetic, but the number can be as high as 20 (Chapter 9, Allergen Survey). In addition to induction and maintenance agents, most patients receive an analgesic drug, an antibiotic for surgical prophylaxis, and at least one anti-emetic. Almost half receive a neuromuscular blocking agent (NMBA). The majority of patients are exposed to chlorhexidine and many are exposed to latex. Other potential trigger agents include radiological contrast and other dyes, intravenous colloid fluids, drugs that affect blood coagulation, and local anaesthetic drugs. Exposure to many of these potentially allergenic agents is not confined to general anaesthesia, and we included patients undergoing procedures with spinal, epidural or local anaesthesia under the care of an anaesthetist, as well as monitored anaesthesia care.

Why do some patients experience perioperative anaphylaxis and not others?

Most anaphylaxis is allergic and, characteristically, the patient's immune system has been sensitised to the same substance during a previous uneventful exposure. Sometimes it is only necessary for the patient to have been exposed to a critical small part of the molecular structure of the trigger agent – the epitope or 'antigenic determinant'.

The majority of patients who experience NMBA-induced anaphylaxis have not had previous exposure, but have been sensitised to a particular epitope which is found in many everyday products. A similar process occurs with Patent Blue dye which may be injected into the tissues to show up lymph nodes during breast surgery. Unfortunately, neither previous uneventful anaesthesia nor the absence of a previous anaesthetic guarantee that perioperative anaphylaxis will not occur.

How is perioperative anaphylaxis treated?

We wished to know how perioperative anaphylaxis is managed in the UK, and whether published guidelines are being followed. Our findings are described in Chapter 11, Immediate management and departmental organisation.

Adrenaline is the mainstay of the treatment of anaphylaxis, and is recommended in all published guidelines. Anaesthetists are very familiar with the range of drugs used routinely to support the blood pressure and relieve bronchospasm, but administration of adrenaline may be outside their 'comfort zone', and an apparent reluctance to administer adrenaline has been described in Denmark (Garvey 2011). We discuss this phenomenon in Chapter 11. Liberal quantities of intravenous fluids are required to restore circulating blood volume and cardiac filling, but there is little published information on the volumes of fluid used in practice.

What did we do in NAP6?

In order to understand perioperative anaphylaxis, we adopted an inclusive approach, with anaesthetists, allergists, clinical immunologists, patient group representatives, and other relevant parties working together, both in the steering group and in the case-review panel. We set up a network of Local Coordinators, one based in every UK NHS hospital, who managed the study locally. We then used this network to collect detailed, anonymised case reports for a one-year period via a secure web-based registry. Each submitted case remained entirely anonymous and was subjected to a series of structured reviews by a multidisciplinary panel to extract the quantitative and qualitative learning on which this report is based. The project methods are discussed in full in Chapter 5.

There were multiple components to NAP6. The first component was a baseline survey of anaesthetists' experiences and perceptions of perioperative anaphylaxis, including the decisions anaesthetists make to avoid anaphylaxis (Chapter 7). In the second part we captured details of waiting times, investigation pathways, and adherence to published guidelines in a survey of specialist allergy clinics investigating suspected perioperative anaphylaxis (Chapter 13). An anaesthetic Activity Survey (Chapter 8) characterised anaesthesia service provision, surgical specialty case-load, and working patterns. This is useful in understanding elements of institutional preparedness, such as the levels of seniority of anaesthetists delivering direct patient care, and how this varies during the working week and across weekends. Estimates of incidence, and risk of anaphylaxis with particular agents, can be made only if the number of exposures are known, and, to that end, the third part of NAP6 was a quantitative survey of patients' exposure to potentially allergenic drugs and other substances during anaesthesia (Chapter 9). The final, and perhaps most important element, was a one-year registry of cases.



What did we find and how can NAP6 help patients?

The findings of all elements of NAP6 are summarised in Chapter 6, Summary of Main Findings relating to particular trigger agents and patient groups are described in further detail in Chapters 10 to 21. A flavour of our findings is provided in the paragraphs below.

Where several alternative anaesthetic drugs are available, some anaesthetists may avoid particular drugs because of perceptions of a high likelihood of triggering perioperative anaphylaxis. These perceptions may or may not be founded in fact. We discovered that avoidance of drugs as a result of perceived anaphylaxis risk is not always based on evidence.

The multidisciplinary NAP6 panel reviewed more than 300 cases of suspected perioperative anaphylaxis and included 266 in the final analysis. Emphasis was placed on assessing quality of management, both by the team providing initial clinical care and by the allergy clinic. We used national guidelines to inform our assessment process wherever possible. As you will read, clinical management was not faultless (Chapter 11). We highlight ways in which improvements can be made, and provide information on setting up anaesthetic anaphylaxis treatment and investigation packs, as well as providing templates for written communication with the patient and their general practitioner. We also suggest ways in which departments of anaesthesia can help by appointing departmental lead anaesthetists with defined responsibilities.

NAP6 received extensive details of the investigations performed by the specialist allergy clinics, and the tests performed and their interpretation were scrutinised by the panel's Allergists and Clinical Immunologists. The quality of investigation and of communication with the patient and the referring team were analysed. The NAP6 review panel did not always agree with the diagnosis made by the allergy clinic or the information given to patients, and this is discussed in Chapter 14, Investigation.

Most previous studies have found that neuromuscular blocking agents (NMBA) are the most common cause of perioperative anaphylaxis. An important finding of NAP6 was that antibiotics are now the most common trigger of anaphylaxis during anaesthesia (Chapter 15, Antibiotics). Antibiotics are administered for prophylaxis against surgical infection in almost 60% of all surgical procedures. Antibiotic stewardship is becoming increasingly important: accelerating antibiotic resistance may even restrict the feasibility of some surgical procedures in the future.

Another notable finding of NAP6 was that the highest risk among the antibiotics was not with penicillins, which are widely prescribed in primary care, but with teicoplanin, a long-acting antibiotic that is only given as an injection, mainly in hospital. Teicoplanin is often a replacement for penicillin in patients who give a history of penicillin allergy, and there are several recent reports of perioperative anaphylaxis caused by this antibiotic (Savic 2017). Most patients who give a history of penicillin allergy are not in fact allergic, and we discuss how 'mis-labelling' could be reduced by better training and communication in the healthcare setting.

The provision of allergy services in the UK has been the subject of several reports which have highlighted the prevailing 'postcode lottery' in the availability of specialist allergy clinics (Select Committee on Health 2003; Royal College of Physicians, 2010). We wished to obtain a UK-wide view of the provision of NHS allergy clinics for the investigation of perioperative anaphylaxis in adults and children, and NAP6 included a detailed national survey of these services, the findings of which strongly support the need for change (Chapter 13, Allergy clinic baseline survey).

We were interested to discover whether presentation, management and adverse effects differ in the obstetric population and in children, as well as identifying any differences in the way these cases are investigated. Our findings are described in Chapter 20 and Chapter 21.

We followed patients through the acute event and into the postoperative period. Patients have a right to high standards of continuing care and we recorded length of stay in hospital and explored the use of critical care services, especially the need for continuing cardiovascular and respiratory support as well as the frequency with which patients had to be transferred to a different hospital for critical care (Chapter 22, Critical care).

More than 1.5 million surgical procedures are performed in independent sector hospitals each year in the UK (Leys 2014), suggesting that approximately a third of cases of perioperative anaphylaxis could be expected to occur in that setting. We invited independent (non-NHS) UK hospitals to contribute case reports to NAP6. Our, somewhat unexpected, findings are described in Chapter 23.

By recording detailed information about all aspects of perioperative anaphylaxis, our ambition is to reinforce best practice and stimulate the introduction of new practices, with the aims of improving clinical management of the acute event, enhancing communication with patients, and strengthening the quality of the specialist allergy services to which patients are referred for investigation after the event.

Improvements in patient care can be achieved only by making detailed recommendations for change. The NAP6 panel makes more than 100 recommendations at national, institutional and individual levels, ranging from how UK specialist allergy clinic services should be structured, to the volume of IV fluids that should be administered during resuscitation. While some of these reiterate existing guidance, it is important to note that all recommendations are based directly on the findings of the data reviewed within NAP6.

Patients expect that all doctors and nurses should have at least basic training in allergy. Allergy-training of medical and nursing staff is patchy, and formal training in allergy history-taking seems to be uncommon at the undergraduate level. We wished to establish to what extent the preoperative allergy history was relevant to perioperative anaphylaxis; could more focused history-taking or better health records have prevented life-threatening reactions?

Immediate management of very uncommon life-threatening incidents is challenging. Anaesthetists can expect to see, on average, fewer than one case of perioperative anaphylaxis every seven years (Kemp 2017). It is particularly important, therefore, that anaesthetists' training is up-to-date, and that guidelines for immediate management are immediately available at all anaesthetising sites. NAP6 recorded real-life availability and use of guidelines and algorithms during the management of perioperative anaphylaxis, as well as assessing clinical management in a structured and detailed fashion.

We were particularly interested in how hypotension and cardiac arrest are being managed in practice (Chapter 12). National guidelines on cardiopulmonary resuscitation (CPR) in cardiac arrest are well known (Soar 2015), but some of the parameters within the guidelines such as 'signs of life' are not applicable to anaesthetised patients who are unable to respond. There is little published guidance on the blood pressure below which CPR should be initiated during anaesthesia, and expert opinion was sought by the NAP6 review panel before setting our threshold. We expect to generate debate and we look forward to future discourse on this important subject.

Outcomes of perioperative anaphylaxis have been poorly studied in the past, and NAP6 sought to record adverse sequelae of all types. We wanted to know whether any aspects of immediate management, such as drugs given in resuscitation or subsequent admission to a critical care unit, affected the likelihood of adverse health consequences. We were also interested to know how often surgery is abandoned as a result of anaphylaxis, and what arrangements are then made to reschedule urgent surgery. When urgent surgery is abandoned it should be rescheduled without delay. This is possible even before the identity of the trigger is known, and we set out a clear and safe plan for providing anaesthesia in these circumstances – to our knowledge the first of its kind to be published.

Patients have a right to expect that their suspected perioperative anaphylactic reaction will be investigated promptly and expertly, so that they are aware of the drugs and other substances they can receive safely in the future, and those they should avoid. We hope our findings and recommendations will lead to quality enhancements and an improved patient experience.

Individual and organisational learning from critical events can only happen if they are reported and investigated at hospital level. NAP6 recorded whether events had been reported to Trust incident-reporting systems, and by whom. Reporting to the Medicines & Healthcare products Regulatory Agency through the Yellow Card Scheme is central to pharmacovigilance: our findings were disappointing and are discussed in Chapter 24.

Finally, we would like to thank those who have made this report possible. The National Audit Projects of the Royal College of Anaesthetists rely entirely on case reports and survey returns submitted voluntarily by UK anaesthetists. NAP6 includes data from all UK NHS hospitals, collected survey data from more than 11,000 anaesthetists and patient surveys from 15,000 anaesthetic episodes, and received more than 500 case reports. The level of engagement of anaesthesia community remains very high. This requires significant coordination within hospitals and diligence by individual anaesthetists. We thank all who contributed, particularly the anaesthetists who reported cases, the tireless Local Coordinators, members of the NAP6 panel and the NAP6 Moderator, all of whom gave their limited spare time freely and without complaint.



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