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Perioperative anaphylaxis—management and outcomes in NAP6

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Perioperative anaphylaxis usually presents unexpectedly and, in many cases, with dramatic symptoms requiring prompt recognition and action to ensure the optimal outcome for the patient. Because of the rare occurrence of these events it is difficult for individual anaesthetists to build up experience in treating these reactions. A paper from the 6th National Audit Project (NAP6), which was a survey of anaesthetists' experiences with perioperative anaphylaxis, showed that on average an anaesthetist experiences a case of perioperative anaphylaxis once every 7.25 yr.¹ This issue of the *British Journal of Anaesthesia*, includes five additional reports from NAP6.^{2–6}

The many projects and studies implemented during NAP6 might be of direct benefit to patients by increasing awareness about perioperative anaphylaxis among anaesthetists, allergists, and immunologists. The multidisciplinary working group behind NAP6 addressed many different clinical problems, and the resulting data include a combination of novel findings and confirmation of previous findings regarding the management and outcomes of perioperative anaphylaxis. The focus of this editorial will be on the management and outcomes of perioperative anaphylaxis included in the paper by Harper and colleagues.⁶

The quality of the immediate management of cases of suspected perioperative anaphylaxis was evaluated by a multidisciplinary review panel including anaesthetists, intensivists, allergists, immunologists, and patient representatives.³ Recognition of anaphylaxis was judged as prompt in an impressive 97% of cases and treatment with epinephrine

was prompt, defined as within 10 min, in 83% of cases. However, overall quality of management was judged as 'good' in just 46% of cases, 'good and poor' in 39% of cases, and 'poor' in only 15% of cases. During the review process, management was judged as inadequate in cases where systolic arterial pressure was <50 mm Hg and cardiac compressions were not initiated. This probably contributed significantly to the surprisingly low rate of cases where management was judged as 'good' (46%). This definition has never been used in previous guidelines on perioperative anaphylaxis and, as data on the duration of profound hypotension are not available, in some cases it might be based on a single measurement. In such cases, it could be detrimental to the patient if initiation of cardiac compressions distracts from immediate administration of epinephrine and fluids, the immediate goals in management of anaphylaxis. Anaphylaxis management guidelines were immediately accessible in 86% of cases and, in 60% of cases, Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines were followed.⁷ This underlines the fact that perioperative anaphylaxis is a rare event, and that the availability of guidelines with clear recommendations of management is important.

Pivotal to the treatment of anaphylaxis is prompt administration of epinephrine with correct dosing. For non-fatal cases, the multidisciplinary panel in NAP6 judged that epinephrine was not administered when indicated in 19% of cases; in 11%, epinephrine was not given at all and in 8.4%, it was given late. Thus, a significant proportion of patients did not receive correct treatment with epinephrine. Only a few studies have provided details on treatment with epinephrine, and the NAP6 findings confirm previous observations on epinephrine dosage and administration route.^{8,9} A total of 82%

of cases were treated with epinephrine, and the majority involved administration as an i.v. bolus. There was an increase in mean total dose with increasing severity grade. A median of three doses was given, and median total dose was 200 µg and 500 µg in severity grades 3 and 4, respectively.

Currently, there is no evidence base for correct dosing of i.v. epinephrine for perioperative anaphylaxis. Correct dosing is important, however, as both undertreating and overdosing can have severe implications. In NAP6, no specific recommendation of dose is given, but most anaesthetists followed AAGBI guidelines⁷ or UK resuscitation council guidelines¹⁰ where initial i.v. boluses of 50 µg epinephrine are recommended. The authors found no important complications at this dosing; specifically, no cases of tachyarrhythmias subsequent to epinephrine treatment were reported. There is currently some variation in recommendations for initial bolus doses of i.v. epinephrine in existing guidelines on perioperative anaphylaxis. French guidelines recommend 10–20 µg for grade 2 reactions and 100–200 µg for grade 3 and above.¹¹ The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) guidelines recommend 20 µg for moderate reactions and 100–200 µg for severe reactions.¹² Scandinavian guidelines recommend initial doses of 10–50 µg increased to 100 µg in severe hypotension.¹³ As not all anaesthetists are familiar with the dosing of i.v. epinephrine in anaphylaxis, such differences can lead to confusion in emergency situations. This calls for standardisation of dosing and an increased focus on training in the management of perioperative anaphylaxis, including correct dilution and dosing of epinephrine.

As a result of capillary leakage and massive vasodilatation during anaphylaxis, administration of i.v. fluids is an important part of the immediate management of anaphylaxis. However, in NAP6 fluid management was judged insufficient in one in five cases. This is in line with a previous report from France concerning fatal cases of perioperative anaphylaxis because of neuromuscular blocking agents, which highlights the importance of titrating vascular filling according to haemodynamic parameters as a supplement to treatment with epinephrine.⁹

Antihistamines and corticosteroids were administered i.v. in the majority of cases despite the lack of hard evidence from the literature. Two Cochrane reviews on the effects of antihistamines and corticosteroids in the treatment of anaphylaxis both failed to identify studies that could be included, and thus no recommendations could be made.^{14,15} In NAP6 a logistic regression analysis was performed to evaluate benefit/harm from antihistamine treatment. The outcome of this analysis was not definitive but, for the first time, some benefit of antihistamine treatment could not be ruled out.

A mast cell tryptase value from the time of anaphylaxis provides valuable information for subsequent allergy work-up and is recommended in all guidelines on perioperative anaphylaxis.^{7,10–13} In the UK, three samples for tryptase analysis are recommended:^{7,16} as soon as the patient is stabilised; 1–2 h after symptom onset; and a baseline sample either at 24 h or later (e.g. at the time of allergy investigation). A retrospective four-centre study of tryptase sampling in perioperative anaphylaxis in the UK during 2005–2012 showed that only 38% of patients had all three samples obtained.¹⁷ This highlights the need for increased awareness of tryptase measurements amongst anaesthetists. The NAP6 process itself is likely to have provided increased awareness of several

aspects of perioperative anaphylaxis including sampling of tryptase. The NAP6 authors chose to omit tryptase data from the paper on management and outcomes and instead to include it in a paper covering investigation results, which will provide information on potential improvement in the rates of tryptase sampling during NAP6.¹⁸ It can be challenging for anaesthetists on busy shifts to remember to order and take blood samples, and other guidelines recommend only one sample from the time of reaction (ideally 1–2 h after symptom onset), with a subsequent baseline sample of tryptase for comparison.^{11,13} Access to an anaphylaxis pack or kit containing materials for blood sampling, relevant forms, information on where to send blood samples, and referral forms have been recommended in Scandinavia for >10 yr.¹³ A similar initiative has recently been implemented in the North of England,¹⁹ and this has improved numbers of tryptase samples obtained. NAP6 thus suggests a separate anaesthetic anaphylaxis treatment pack and anaesthetic anaphylaxis investigation pack.

The NAP6 studies include data on outcomes. Of 266 cases investigated there were 40 cases of cardiac arrest leading to 10 fatalities, which translates to a mortality rate of 3.8%. This rate is similar to that observed in a large-scale study in France of severe cases of anaphylaxis to neuromuscular blocking agents that reported a 4.1% mortality rate.⁶ This is in contrast to a study from Western Australia where no deaths from perioperative anaphylaxis were identified over a 10-year period.²⁰ Causes of mortality are likely to be multifactorial. In NAP6 management in fatal cases was prompt in all but one case. Epinephrine was administered in all cases, but fluid resuscitation volumes were relatively low with room for improvement. Increased age, high ASA physical status, morbid obesity, coronary artery disease, and treatment with β -blockers or angiotensin-converting-enzyme inhibitors were all risk factors for fatal reactions. Similar findings were reported in the French study on fatal reactions to neuromuscular blockers.⁶ However, these factors all interact, and the contributions of individual risk factors are not obvious but should be the subject of further research.

Alarming, both in NAP6 and in the French study on anaphylaxis, fatalities were observed even when management was judged as 'good', that is epinephrine was administered promptly in appropriate dosages. Fatalities in the French study even occurred when cardiopulmonary bypass was instituted in nine cases.⁹ These reports indicate that some cases might be refractory to epinephrine treatment and even to cardiopulmonary bypass. Additional treatments for anaphylaxis such as vasopressin and glucagon were rarely used in NAP6 and were mainly used as last resort in patients with cardiac arrest. Although these treatments are suggested in other guidelines,^{11–13} evidence for their use is lacking. Cases not responding to recommended treatments provide a strong incentive for further research into the mechanisms, mediators, and effectors involved in anaphylaxis to define possible new therapeutic approaches.^{21–23}

Data on whether surgery is continued after the immediate management of perioperative anaphylaxis are scarce. A recent study suggests that surgery can be continued in most grade 3 reactions once the patient is stabilised.²⁴ In NAP6, surgery was abandoned in about half of cases, and the multidisciplinary panel considered that continuing surgery was inadvisable in grade 3 and 4 reactions. The decision on whether to continue surgery will always depend on a risk-benefit evaluation in the

individual case including factors such as indication for surgery and comorbidities. The risk of cancelling surgery is that there will be a reluctance to reschedule the procedure before allergy evaluations have been performed, which might lead to detrimental delays, for example, in cancer or emergency surgery. The consequences of continuing or delaying surgery should be the subject of further studies.

NAP6 is the first project providing data on morbidity both physical, such as myocardial infarction or acute kidney injury, but also psychological, such as anxiety, mood, or post-traumatic stress disorder. Whilst data are not complete it still provides an important insight into the long-term consequences of perioperative anaphylaxis in some patients.

To avoid future re-exposure to the culprit allergen subsequent allergy evaluation is mandatory as it is not possible to guess the culprit from multiple simultaneous exposures in the perioperative setting.²⁵ Planning a safe subsequent anaesthetic is possible based on identification of the culprit allergen and of safe alternatives.²⁶ Referral for allergy evaluation and appropriate warning of the patient is therefore important to prevent recurrences. Only 6% of patients underwent further uneventful surgery before being assessed in an allergy clinic, which suggests that communication about the event was adequate.

Improving awareness of perioperative anaphylaxis among anaesthetists could promote prompt diagnosis and correct treatment. The challenge is to achieve adequate experience in the management of perioperative anaphylaxis because of the rarity of this event. Simulation training in perioperative anaphylaxis²⁷ and hands-on practice in diluting epinephrine for paediatric resuscitation²⁸ might be one way to achieve adequate experience by training with regular intervals in a safe environment. Improvements in diagnostic techniques should also facilitate early recognition of intraoperative hypersensitivity reactions.²⁹

Ensuring close collaboration between anaesthetists and physicians undertaking subsequent allergy evaluation is paramount in ensuring safe future anaesthesia procedures for patients. Such collaborations were suggested as early as the 1980s by French, British, and Australian researchers³⁰ and have been implemented widely in France.¹¹ The NAP6 has brought even more focus on the multidisciplinary approach in perioperative anaphylaxis and has identified several important areas for future research. Establishing international collaborations within the field of perioperative anaphylaxis would provide the opportunity for multicentre studies to shed light on some of the questions raised by the NAP6 process and ultimately improving the management of patients suffering these rare but dramatic events.

Authors' contributions

First draft of the manuscript: L.H.G.

Equal contribution to all subsequent revisions of the document: L.H.G., P.M.M.

Declarations of interest

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