

EDITORIAL

Special issue on suspected perioperative allergic reactions

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This edition of the *British Journal of Anaesthesia* incorporates a Special Issue on suspected perioperative allergic reactions. The idea was proposed to the editorial board by one of the authors (PMH) because of the burgeoning literature in this field and the anticipated interest among anaesthetists generated by the results of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists, which reported on the incidence and outcome of perioperative anaphylaxis in the UK.^{1–4} The editorial board agreed on the proposal and the suggestion that the Chair of The European Academy of Allergy and Clinical Immunology (EAACI) task force on perioperative hypersensitivity (LHG) should work with PMH to develop the content. Together, we planned a series of commissioned articles that would form the core of the Special Issue, while a call for papers invited original research submissions. In order to provide an international perspective on current research and opinion in perioperative hypersensitivity reactions, we sought to convene a group of international experts to produce the commissioned content. Recognising the need for a collaboration between anaesthetists and allergists in perioperative hypersensitivity, also highlighted by NAP6, we wanted to include colleagues from relevant specialties. We identified anaesthetists, allergists, and immunologists who had direct clinical experience of assessing and managing patients referred for investigation of suspected perioperative allergic reactions and who had published in the field including currently available international guidelines. We approached, by email, 31 international experts in suspected perioperative allergic reactions of which 17 were anaesthetists and 14 were

allergists or immunologists. Of these, 14 anaesthetists and 10 allergists/immunologists agreed to participate, bringing the group size to 26. All those who declined the invitation did so because they were unable to guarantee the time commitment demanded by the work to be undertaken. The group was named the International Suspected Perioperative Allergic Reaction (ISPAR) group.

The initial work of the group was conducted by email and from this process five topics for special articles were agreed. Two of these topics were related to outcomes of the NAP6 project. NAP6 was unique in that it sought to capture all cases of perioperative anaphylaxis occurring in a large European country.¹ While other groups have collected large series of cases of suspected perioperative hypersensitivity reactions, none has been so systematically collected from such a large denominator of anaesthetic procedures undertaken over such a short period of time. The type of data generated by NAP6 is important in defining the risks of anaphylaxis occurring in the perioperative period and also the risks associated with specific agents as triggers of the reaction. However, one of the intriguing and recurrent observations concerning the epidemiology of perioperative hypersensitivity reactions is the differences reported by different countries. A special article on comparative epidemiology⁵ therefore uses the new data from NAP6 to put in context the UK experience with that reported from elsewhere.

The second special article with direct relation to outcomes of the NAP6 project is an international overview and consensus statement on the management of suspected perioperative allergic reactions.⁶ The NAP6 publications and

previous guidelines have shown differences in recommendations on aspects of management such as the dosing of epinephrine and fluids. The expert group used a formal consensus generating approach to achieve consensus on these and other aspects of the immediate perioperative management of perioperative anaphylaxis. In addition, members of our expert group contributed to providing an overview of relevant and practical information for anaesthetists faced with a patient with a suspected perioperative allergic reaction, based on current literature and expert opinion. While the level of evidence is generally low in the field of perioperative allergy, our expert group included authors of previous guidelines from Scandinavia,⁷ the UK,⁸ France,⁹ Spain,¹⁰ and Australia and New Zealand.¹¹

The next two special article topics arose from the recognition of the limitations of currently available diagnostic tests used in the investigation of suspected perioperative allergic reactions. It is generally accepted that the commonly used investigations (mast cell tryptase, skin prick tests, intradermal tests and *in vitro* tests) lack sensitivity and specificity. Furthermore, better tools are needed for estimating the likelihood that a suspected immediate hypersensitivity reaction was indeed an immediate hypersensitivity reaction (a true positive case) based on clinical information alone. We therefore used a formal consensus generating approach to develop a score for the likelihood of a true hypersensitivity reaction based on clinical information alone and, secondarily, clinical information along with mast cell tryptase changes.¹²

An alternative approach to overcoming problems with currently used diagnostic investigations is examined in the fourth special article. The gold standard test in the investigation of drug allergy (to e.g. antibiotics) is the provocation test. However, provocation testing of drugs used in anaesthesia, such as neuromuscular blocking agents, presents practical challenges and has not been recommended in previous guidelines. The special article summarises the limited published experience of provocation testing with anaesthetic agents and other drugs used during anaesthesia and combines this with a narrative account of the collective views of the group as to how provocation testing could be expanded for the investigation of suspected perioperative allergic reactions.¹³

We deliberately did not include an article on guidelines for the investigation of suspected perioperative allergic reactions. Such guidelines have been produced and recently published by the task force on perioperative hypersensitivity commissioned by EAACI.¹⁴ Several members of this task force also participated in the ISPAR group.

The fifth special article describes the development of an international consensus guideline for the management of surgical patients who have been labelled as penicillin allergic.¹⁵ This is a highly topical and potentially controversial area and we hope that our recommendations can at least make inroads in tackling a problem that contributes to sub-optimal perioperative antibiotic prophylaxis and antimicrobial resistance.

In addition to the commissioned special particles, the expert group identified a series of topics for narrative reviews that would be of interest to the BJA readership. These narrative reviews range from discussion of the molecular mechanisms and pathophysiology of hypersensitivity reactions¹⁶ through clinical topics, such as chlorhexidine allergy¹⁷ and the anaesthetic management of patients with pre-existing allergic conditions,¹⁸ and a review of the use and application of

simulation training in the management of perioperative anaphylaxis.¹⁹

Having established the content of the commissioned material for the special issue, the BJA funded a workshop attended by the lead authors of each of the special articles and representatives from most of the countries contributing members to the expert group. This meeting took place over 2 days in Copenhagen in June 2018, and included presentations of unpublished data, discussion of the methodological approach to developing consensus, agreement of the detailed coverage of each special article, and identification of gaps in evidence requiring the application of formal consensus development. An additional outcome of the workshop was a recognition that the terminology and definitions used in the field of drug hypersensitivity were potentially confusing, especially for non-experts in the field. We therefore recommend the editorial by Sabato and colleagues²⁰ as useful reading to accompany the other articles in this special issue.

Finally, those participating in the ISPAR group recognised the educational and intellectual value of the BJA forum, which uniquely brought together anaesthetists and allergists/immunologists working and researching in perioperative hypersensitivity reactions from all over the world. We recognise the potential future benefits of continuing this international collaboration and broadening its membership in order to extend the opportunities it provides to other colleagues working in the field. To this end we would like to extend the invitation to international societies in the field of anaesthesia and allergy to support this collaboration.

Authors' contributions

Both authors conceived, drafted, reviewed, and revised drafts of the manuscript and approved the final version.

Declarations of interest

LHG is a consultant and adjudication committee member for Merck, NJ, USA and a consultant and adjudication committee member for Novo Nordisk, Denmark. PMH is an editorial board member of *British Journal of Anaesthesia*.

References

1. Cook TM, Harper NJN, Farmer L, et al. Anaesthesia, surgery, and life-threatening allergic reactions: protocol and methods of the 6th National Audit Project (NAP6) of the Royal College of anaesthetists. *Br J Anaesth* 2018; **121**: 124–33
2. Marinho S, Kemp H, Cook TM, et al. Cross-sectional study of perioperative drug and allergen exposure in UK practice in 2016: the 6th National Audit Project (NAP6) Allergen Survey. *Br J Anaesth* 2018; **121**: 146–58
3. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
4. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 172–88
5. Mertes PM, Ebo DG, Garcez T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.01.027>

6. Garvey LH, Dewachter P, Hepner DL, et al. Management of suspected immediate perioperative allergic reactions—an international overview and consensus recommendations. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.04.044>
7. Krøigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
8. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
9. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2011; **21**: 442–53
10. Laguna JJ, Archilla J, Dona I, et al. Practical guidelines for perioperative hypersensitivity reactions. *J Invest Allergol Clin Immunol* 2018; **28**: 216–32
11. Kolawole H, Marshall SD, Crilly H, Kerridge R, Roessler P. Australian and New Zealand anaesthetic allergy group/ Australian and New Zealand College of anaesthetists perioperative anaphylaxis management guidelines. *Anaesth Intensive Care* 2017; **45**: 151–8
12. Hopkins PM, Cooke PJ, Clarke RC, et al. Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.02.029>
13. Garvey LH, Ebo D, Krøigaard M, et al. The use of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions: current status. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.03.018>
14. Garvey LH, Ebo D, Mertes PM, et al. Position Paper on the investigation of perioperative immediate hypersensitivity reactions—an expert consensus from the EAACI task force on perioperative hypersensitivity. *Allergy* 2019. <https://doi.org/10.1111/all.13820> (Accepted March 2019)
15. Savic LC, Volcheck GW, Khan DA, et al. Management of the surgical patient with a label of penicillin allergy: narrative review and consensus recommendations. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.01.026>
16. Ebo DG, Clarke RC, Mertes PM, Platt PR, Sabato V, Sadleir PHM. Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis: a narrative review. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.01.031>
17. Rose MA, Garcez T, Savic S, Garvey LH. Chlorhexidine allergy in the perioperative setting: a narrative review. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.01.033>
18. Dewachter P, Kopac P, Laguna JJ, et al. The anaesthetic management of patients with pre-existing allergic conditions: a narrative review. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.01.020>
19. Kolawole H, Marshall SD, Hepner DL, Guttormsen AB, Krøigaard M. Use of simulation to improve management of perioperative anaphylaxis: a narrative review. *Br J Anaesth* 2019. <https://doi.org/10.1016/j.bja.2019.01.035>
20. Sabato V, Platt PR, Garcez T, Cooke PJ. Suspected perioperative allergic reactions: nomenclature and terminology. *Br J Anaesth* 2019