

CLINICAL INVESTIGATION

Outcome of repeat anaesthesia after investigation for perioperative anaphylaxis

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Data were presented in part at the British Society for Allergy and Clinical Immunology Annual Meeting, 2014.¹

Abstract

Background: Perioperative anaphylaxis (POA) is infrequent, but remains an important and potentially life-threatening complication of general anaesthesia. The diagnostic uncertainty surrounding the investigation of anaesthetic allergy poses numerous challenges. We aimed to inform practice by auditing the outcomes of repeat anaesthesia, after an investigation for previous POA.

Methods: One-hundred and seventy-four subjects were investigated after suspected POA between December 2002 and August 2015. Outcome data were obtained for a total of 70 patients who underwent repeat anaesthesia after investigation in the drug-allergy clinic.

Results: Sixty-seven out of the 70 patients studied underwent repeat anaesthesia without further complications. Three individuals experienced a further episode of anaphylaxis. In two cases, incomplete referral information led to the offending drugs being omitted from initial testing. The third was found to have underlying systemic mastocytosis (SM).

Conclusions: In our cohort, the incidence of repeat anaphylaxis after a comprehensive assessment in the drug-allergy clinic for suspected POA was 4%. Important risk factors include the completeness of referral information provided to the assessor and the role of exacerbating disorders, particularly SM.

Keywords: anaesthetic allergy; mast cells; perioperative anaphylaxis

Anaphylaxis is a rare but serious complication of general anaesthesia (GA). Anaphylactic reactions associated with anaesthesia have the potential to cause significant morbidity (with 2% of cases suffering from long-term neurological sequelae) or mortality (3–6% of cases^{2,3}).

Whilst the true incidence of perioperative anaphylaxis (POA) is largely unknown, previous studies have reported rates of between 1 in 3000 and 1 in 20,000.^{2,4–7} By extrapolating these data, it is estimated that, in the UK, between 175 and 1000

episodes of anaphylaxis occur in relation to anaesthesia each year.^{8,9} However, this figure is likely to under-represent the true incidence of anaesthetic-related anaphylaxis. Indeed, data collected from 4595 anaesthetics, performed over 12 hospitals in a large region of the UK, found that as many as 1 in 353 cases met referral criteria for further investigation of suspected POA.¹⁰

The recognition of POA, followed by the subsequent identification and avoidance of the offending drug trigger, is

Editorial decision: March 1, 2018; **Accepted:** March 1, 2018

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Editor's key points

- General anaesthesia for patients with a history of perioperative anaphylaxis may be problematic, partly because of the limitations of allergy testing.
- In this retrospective study, general anaesthesia was uneventful in 67 out of 70 patients investigated previously for perioperative anaphylaxis.
- In two cases where further anaphylaxis occurred, testing was incomplete because referral information was lacking.
- A further case of repeat anaphylaxis occurred in a patient with systemic mastocytosis.
- These data emphasise the importance of good communication between anaesthetists and allergy specialists.

essential in preventing recurrence during future anaesthetics. However, the investigation of suspected POA is complex, owing to the concurrent administration of both anaesthetic and non-anaesthetic agents during the induction phase, coupled with the lack of reliable and validated tests available for drug-allergy testing.³ Skin prick and intradermal tests remain the mainstay of allergy testing in this area, but are imperfect for diagnostic purposes because of their limited sensitivity and specificity. Indeed, the consequences of both false-positive and false-negative results are apparent, ranging from the unnecessary avoidance of a drug to erroneous administration of a potentially life-threatening agent.³ Furthermore, the timing of skin tests may be critical. False negatives may occur if performed too early because of temporary depletion of immunoglobulin E (IgE) antibodies. Conversely, the sensitivity of skin tests may decline over time should testing be delayed.³ Contrary to other areas of allergic disease, where *in vitro* diagnostic tests are under constant development, the range of drugs that can be tested for in routine laboratory assays is limited. Tests capable of measuring specific IgE (sIgE) to neuromuscular blocking agents (NMBAs), which account for 60–70% of all anaesthetic allergy, remain largely unavailable.^{3,11} In other areas of allergic disease, establishing tolerance through double-blind placebo-controlled challenges is fundamental to the diagnostic process. However, sequential drug challenges are impractical and risky for most patients with POA.

Despite these pitfalls, the expert and timely investigation of anaesthetic allergy is essential, particularly in those in whom surgery has been abandoned, in order to ensure safe and satisfactory outcomes from repeat anaesthesia. The aim of this study was to audit outcomes after repeat anaesthesia in a cohort of patients previously investigated for POA in order to quantify risk and improve anaesthetic outcomes for individuals with suspected drug allergy. Data were presented in part at the British Society for Allergy and Clinical Immunology annual meeting in 2014.

Methods**Procedure for allergy assessment**

The investigation in the drug-allergy clinic is based on a detailed referral letter, completion of the referral *pro forma* of the Association of Anaesthetists of Great Britain and Ireland (AAGBI), and

analysis of anaesthetic charts.⁹ Patients are skin tested, as appropriate, against the anaesthetic drugs they received at induction alongside any antibiotics, colloidal fluids, antiseptic solutions, and latex to which they were exposed. One or more alternative NMBAs are tested alongside the index NMBA administered before anaphylaxis, to enable the establishment of a safe alternative. Skin prick testing (SPT) is performed with a 1:10 dilution of each drug in solution, followed by a 1:1 dilution if the former is negative. Intradermal testing (IDT) with 1:10 solutions (or recommended non-irritant concentrations) is carried out if SPT is negative. Drug-specific IgE is requested where available. If skin/intradermal tests and sIgE are negative, the advice for avoidance of a particular drug is based on a careful analysis of the temporal relationship of the drugs administered in relation to the onset of anaphylaxis along with consideration of the propensity of certain drugs to cause such reactions.

Study design

This is a retrospective cohort analysis of all patients attending the drug-allergy clinic for investigation of suspected POA between the periods of December 2002 and August 2015. Because this study focused on the outcome of a recognised investigatory pathway, it constituted a service evaluation, and hence, formal ethics approval was not sought. The notes of patients whose surgery was abandoned after POA were reviewed to determine whether the recommendations set out by the drug-allergy clinic had been followed and the outcome of any further anaesthetic encounters. In those in whom notes were not available, information was sought via written correspondence with the referring anaesthetist.

Data collection

Information relating to the initial episode of anaphylaxis was recorded for all patients investigated for suspected POA, and included the name of the surgical procedure, World Allergy Organization (WAO) grade of anaphylaxis, timing of serum tryptase concentrations, interval between reaction and allergy assessment, results of skin prick and IDT plus sIgE where available, and the advice given to the referring anaesthetist regarding future anaesthetics. Follow-up data for repeat anaesthesia included name of surgical procedure, anaesthetic agents administered, and whether or not the patient had repeat anaphylaxis.

Sample size

As this was a retrospective observational study in a random group of patients referred for investigation of suspected POA, we were not intending to generate or test a hypothesis. Consequently, power calculations would not be possible or appropriate.

Results**Study cohort**

One-hundred and seventy-four individuals were investigated for suspected POA in the drug-allergy clinic between December 2002 and August 2015. Surgery had been abandoned as a result of anaphylaxis in 86 of these patients. Follow-up data relating to repeat anaesthesia were obtained for 59 of the 86 patients in whom surgery was abandoned, plus an

additional 11 patients in whom the initial surgery resulting in anaphylaxis continued to completion, but who were anaesthetised for a different procedure at a later date. Fig. 1 shows the inclusion/exclusion criteria for this study.

Patient characteristics

The mean age of the patients in this study was 52.1 yr (range: 2–84 yr). One-hundred and twenty-two (70.1%) of patients were female. The distribution according to age is as follows: 0–10 yr=1, 11–20 yr=4, 21–40 yr=34, 41–60 yr=73, 61–80 yr=58, and 81–100 yr=4. The index surgery was performed under GA in 168 patients (97%), whilst the remaining

six patients underwent spinal anaesthesia. Seven of the 70 follow-up patients had a spinal anaesthetic, with the rest undergoing repeat GA. Within the study cohort, 159 patients (91%) met the WAO criteria for diagnosing anaphylaxis. The remaining 15 subjects were included in the study because their history was strongly suggestive of IgE-mediated hypersensitivity, with symptom onset temporally related to drug administration and all other possible causes of intraoperative morbidity excluded. The peak serum tryptase concentration, measured between 0 and 6 h after the onset of anaphylaxis, was recorded in 127 (73%) of study patients, with a median peak serum tryptase concentration of 21.6 $\mu\text{g litre}^{-1}$ (IQR=8.75–44.2).

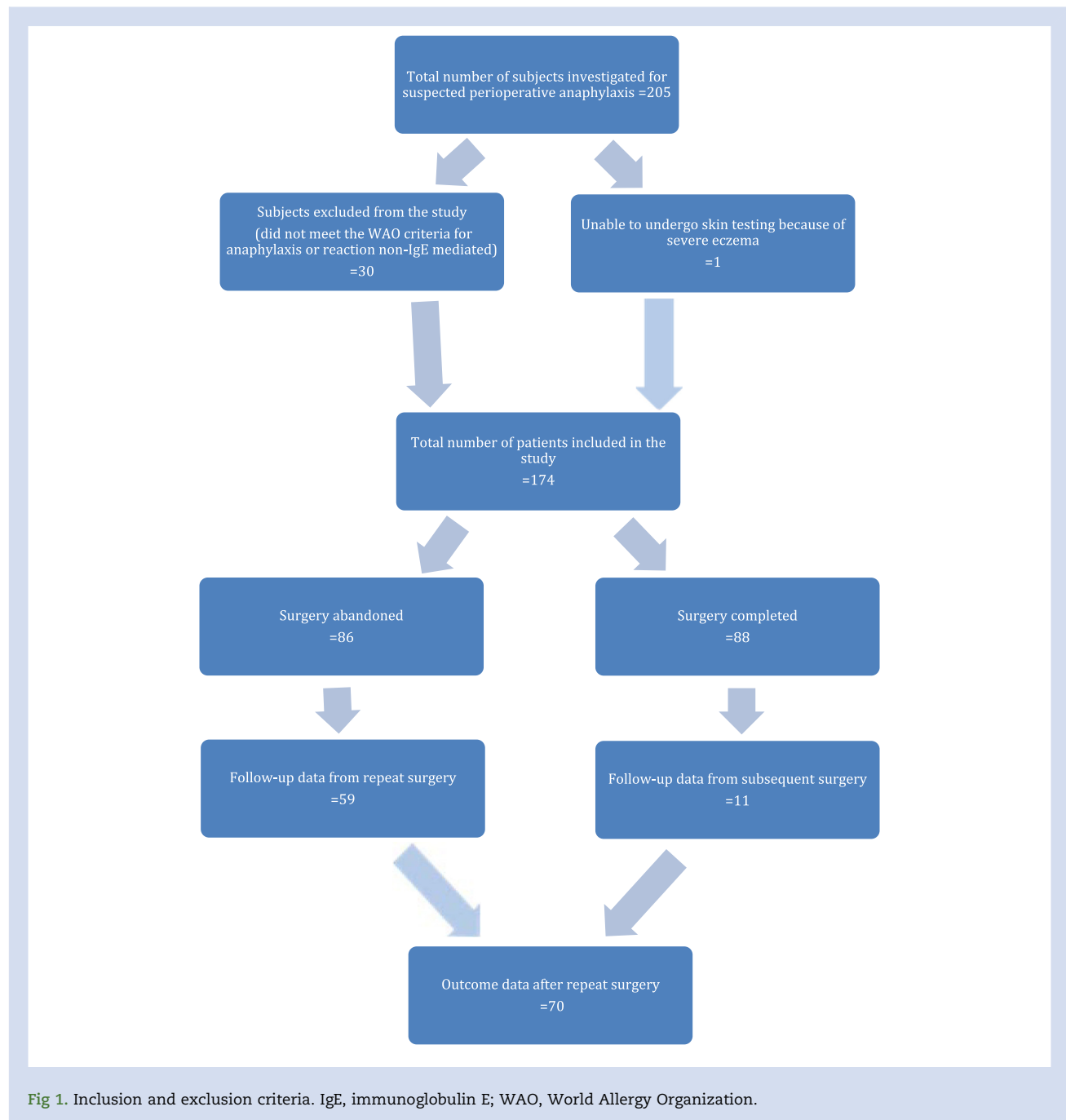


Fig 1. Inclusion and exclusion criteria. IgE, immunoglobulin E; WAO, World Allergy Organization.

Study findings

Results of allergy assessment

As expected, and in keeping with previous reports, NMBAs, either singly or in combination with other drugs, accounted for the majority of cases of anaphylaxis, followed by β -lactam antibiotics. Fig. 2 shows the frequency and distribution of drugs causing POA in this study cohort. The total number of drug triggers (200) exceeds the number of study patients (174) because of multiple drug triggers being implicated in 26 individuals.

Based on a combination of skin testing (prick/intradermal) and sIgE measurement, a trigger for anaphylaxis was identified in 127 out of 174 patients (73%) investigated in the drug-allergy clinic after POA. For those patients who went on to have repeat anaesthesia, an allergic trigger was identified in 79% (55 out of 70) (Table 1).

Underlying the poor predictive value of skin testing for the investigation of anaesthetic allergy, the agent responsible for triggering anaphylaxis could only be identified in 43% (75 out of 174) of patients using SPT alone (Table 1). However, the most challenging group, containing almost one-third of the patient cohort (27%), was that in whom all allergy tests were negative. In this situation, our advice for the avoidance of a particular drug is supported by a careful analysis of the temporal relationship of the drugs administered to the onset of anaphylaxis along with consideration of the propensity of certain drugs to trigger hypersensitivity reactions.

Outcome of repeat anaesthesia

The analysis of follow-up data revealed that the drug implicated in the index episode of anaphylaxis was excluded from subsequent anaesthetic regimens in all cases. For NMBAs, the drugs used at initial anaesthetic induction and on re-challenge at repeat anaesthesia are presented in Table 2.

Table 1 Number of patients (out of a total of 174 patients investigated in the drug-allergy clinic) in whom a drug trigger for their episode of perioperative anaphylaxis was identified as a result of positive SPTs, IDTs, or sIgE, either alone or in combination. Values in brackets indicate number of patients with positive allergy tests that went on to have repeat anaesthesia. IDT, intradermal testing; sIgE, drug-specific immunoglobulin E; SPT, skin prick testing

Investigation	Number of patients
SPT	75 (31)
IDT	10 (4)
sIgE	9 (2)
SPT+sIgE	25 (13)
IDT+sIgE	0 (0)
SPT+IDT	5 (3)
SPT+IDT+sIgE	3 (2)
Total	127 (55)

In the cohort of patients in whom follow-up data were available, repeat anaesthesia proceeded uneventfully, with no further anaphylaxis, in 96% of cases (67 out of 70 cases).

Three individuals had a further episode of anaphylaxis when re-exposed to GA. In all three, an NMBA was thought to have been the trigger for their initial episode of anaphylaxis. In one of these patients, our advice was based on a positive intradermal test to atracurium after negative SPT at both 1:10 and 1:1 concentrations. The remaining two patients had entirely negative skin and intradermal tests, (and sIgE tests where applicable), and our advice was based on the chronological order of events as set out in the anaesthetic charts. The index NMBA was subsequently avoided in all three cases. After their second episode of anaphylaxis, the review of two of the cases (Case 1 and Case 2) revealed that inadequate information had been provided by the referring anaesthetist, with the

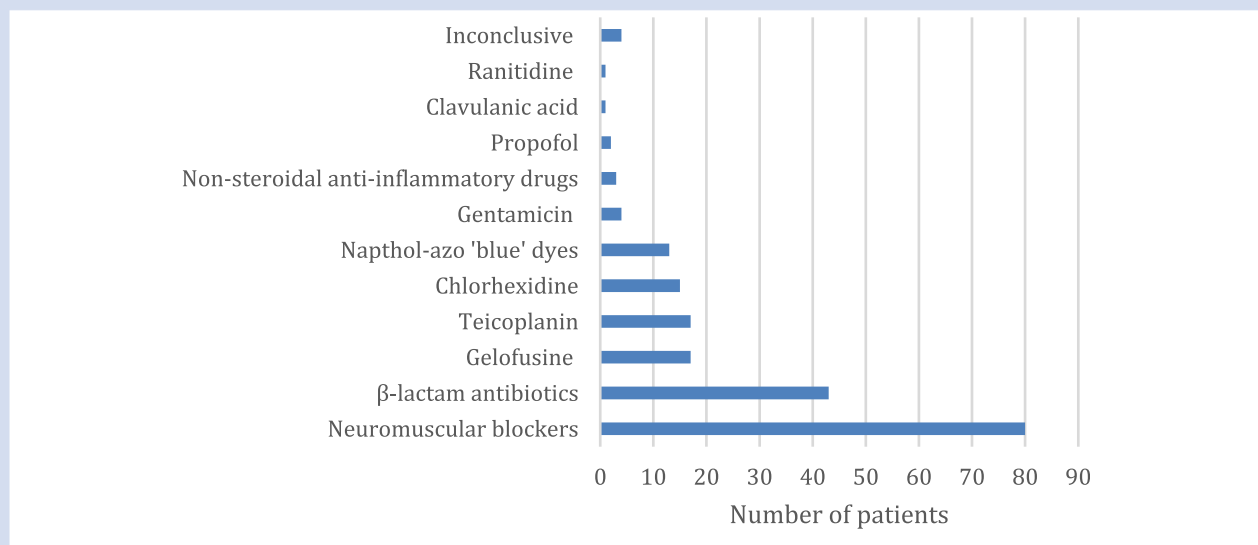


Fig 2. Drugs causing index episode of anaphylaxis for all patients investigated for perioperative anaphylaxis between December 2002 and August 2015. The total number of drug triggers (200) exceeds the total number of patients included in the study (174) because of multiple drug triggers being identified in 26 patients.

Table 2 Neuromuscular blocking agents (NMBAs) used during index reaction and on repeat anaesthesia. Outcome of repeat anaesthesia is indicated (N, no further anaphylaxis; A, repeat anaphylaxis (number in brackets denotes case number with reference to main article). AT, atracurium; CIS, cisatracurium; NK, not known; PAN, pancuronium; RO, rocuronium; SUX, suxamethonium; VE, vecuronium

[illegible]

offending drugs, chlorhexidine (Case 1) and gelofusine (Case 2), being omitted from their original referral letter, and thus, not considered during the initial testing. Allergy to these agents was confirmed on follow-up skin testing performed during a second attendance to the drug-allergy clinic. The third patient (Case 3) went on to have a total of three episodes of anaphylaxis more than a period of 7 yr, spanning a number of surgical procedures. Despite demonstrating a normal baseline serum tryptase of $13.2 \mu\text{g litre}^{-1}$ (normal range: $0\text{--}16 \mu\text{g litre}^{-1}$) after her initial episode of anaphylaxis, her repeated reactions to structurally non-related drugs and failure of tryptase to normalise after the third episode raised the suspicion of underlying systemic mastocytosis (SM). This has subsequently been confirmed on bone-marrow biopsy.¹²

Discussion

Our study has demonstrated that repeat anaesthesia was successful in 96% of patients who were investigated in the drug-allergy clinic for suspected anaesthetic allergy.

Several aspects have emerged as significant contributory factors influencing the risk of recurrence during future anaesthetics. Firstly, our findings highlight the importance of a comprehensive referral letter, accompanied by a copy of the anaesthetic chart, in identifying potential drug triggers so that allergy testing may be completed without vital omissions. This underlines the critical role of the anaesthetist in referring a patient for allergy testing after an episode of anaesthetic-related anaphylaxis. In the UK, guidelines for recognising, reporting, and referring suspected cases of POA have been compiled by the AAGBI to encourage good practice in this area.^{9,13}

This study also draws attention to the importance of excluding underlying SM in any patient experiencing multiple episodes of anaphylaxis. SM may pose a diagnostic challenge particularly in the absence of cutaneous or systemic features of mast-cell hyperactivity. Furthermore, it is important to note that having a serum basal tryptase concentration that falls below the upper limit of normal does not exclude mastocytosis, as exemplified by Case 3 in our series.¹⁴ Although the true prevalence of SM in this population is unknown, it is likely

that a proportion of individuals with anaesthetic allergy will have SM.^{15,16}

Our results are in keeping with a recently published US cohort of 73 patients, investigated more than a 10 yr period. In this cohort, a total of 45 out of 47 patients (96%) tolerated repeat anaesthesia without complications.¹⁷ Other studies have documented repeat anaphylaxis in 1–4% of patients with suspected anaesthetic allergy.^{18–21}

Discrepancies between studies looking at the incidence of repeat anaphylaxis during anaesthesia will be influenced by study size and design, and the differing strategies used by individual centres for investigating drug allergy. Indeed, there are no standardised protocols for investigating anaesthetic drug allergy, and variable drug concentrations may be used for skin testing between centres.¹¹ This is a particular problem with NMBAs, which account for approximately 50% of anaphylaxis during GA.⁶ There is a disagreement regarding the sensitivity of skin tests to NMBAs and the optimal concentrations to be used to avoid false-positive and negative results.³ The concentrations of NMBAs used for skin testing are important. One study reported between 40% and 50% of healthy volunteers were positive to SPT with undiluted vecuronium and rocuronium highlighting the direct histamine-releasing effect that these agents can have on mast cells.²² Furthermore, cross-reactivity between structurally related NMBAs is reported in up to 65% of skin tests.³ This prompted the recent UK guidelines to recommend skin testing with all available NMBAs and i.v. anaesthetics.¹¹ However, the clinical significance of cross-reacting skin tests to NMBAs is unknown.¹¹ Porri and colleagues²³ demonstrated that the prevalence of NMBA sensitivity (as defined by a positive skin test to one or more NMBAs in the absence of a history of drug allergy) in the general population was as high as 9.3%. In another study, the prevalence of positive skin tests to NMBAs was 2.8% in an unexposed surgical population.²⁴ The high false-positive rate of skin testing with NMBAs suggests that extensive, blanket testing with NMBAs is likely to generate results that are unhelpful in clinical management. Certainly, in our experience, the low rate of anaphylaxis in our patient group indicates that skin testing with the index NMBA plus one or more structurally unrelated agents is sufficient, particularly as the high negative predictive rate of skin testing with NMBAs has been demonstrated.²⁰ Nevertheless, utmost vigilance needs to be exercised in view of rare reports of NMBA-induced anaphylaxis in patients receiving an alternative NMBA chosen on the basis of negative skin tests.²⁵

We acknowledge several limitations to this study. Firstly, the study includes a minority of patients (9%) who did not meet the WAO criteria for anaphylaxis. However, as previously discussed, these patients were included because of a strong clinical suspicion for IgE-mediated hypersensitivity. Indeed, it is often the case that some of the conventional symptoms of anaphylaxis (e.g. cutaneous features) may be hidden in patients who are draped during surgery, and therefore, under-reported. A high index of suspicion of possible POA is required in this setting, even in the absence of other diagnostic criteria. We also acknowledge that in 17 of the follow-up patients, repeat anaesthesia had been performed before their assessment in the clinic. However, sensitisation to the suspected drug trigger that was avoided during repeat surgery was subsequently confirmed on skin testing, enabling further validation of our testing procedures. The retrospective nature of this study meant that data could not be captured for

all patients investigated for suspected POA in our clinic, in some cases because of the unavailability of notes or anaesthetic charts, but also because of a significant proportion of patients undergoing procedures in different hospital Trusts.

Overall, despite these limitations, the systematic collection of data on the outcome of repeat anaesthesia in this first UK-based study and its congruence with results reported by others^{17–21} validates our approach to the investigation of POA. Outcome data are important in a field, such as drug allergy, where there is much diagnostic uncertainty and where the risk of erroneous advice is significant. For patients attending our clinic, it enables us to quantify future risk of anaphylaxis after an assessment in our clinic and provides a benchmark for others practising in this area. This study also demonstrates how an effective communication between the immunology and anaesthetic departments, as recommended by the AAGBI, can optimise patient care.

Authors' contributions

Study supervision: S.A.M.

Study design: S.A.M., R.C.P., J.M.

Data collection: J.M., S.A.M., S.C.

Data interpretation: J.M., S.A.M., R.C.P.

Writing of manuscript: J.M., S.A.M.

Review of manuscript: S.A.M., R.C.P., J.M., S.C.

Declaration of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank their anaesthetic colleagues for providing feedback on patients undergoing repeat anaesthesia after an investigation in the drug-allergy clinic. The authors also thank Dr Brian Shine for statistical advice.

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Handling editor: J.P. Thompson