

Original Article

Anaesthesia-associated hypersensitivity reactions: seven years' data from a British bi-specialty clinic*

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Summary

Our bi-specialty clinic was established to systematically investigate patients with suspected peri-operative hypersensitivity reactions. Four hundred and ten patients were studied; 316 following an intra-operative reaction ('postoperative' group) and 94 with a previous history of reaction, referred before undergoing anaesthesia ('pre-operative' group). In the postoperative group, 173 (54.7%) were diagnosed with IgE-mediated reactions: 65 (37.6%) to neuromuscular blocking drugs; 54 (31.2%) antibiotics; 15 (8.7%) chlorhexidine and 12 (6.9%) patent blue dye. Reactions were severe in 114 patients (65.9%). All reactions to patent blue dye were severe. We identified IgE sensitisation in 22 (13.2%) cases with isolated mucocutaneous reactions. Only 173 (54.7%) patients had serum tryptase samples taken. Referrers' suspected causal agent was confirmed in only 37.2% of patients. Of 94 patients reviewed 'pre-operatively', 29 (30.8%) were diagnosed with IgE-mediated hypersensitivity reactions, reinforcing the importance of investigating this group of patients. Knowledge of the range of causative agents identified in our study should guide the investigation of suspected peri-operative hypersensitivity reactions.

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Introduction

A joint anaesthetist/allergist clinic was established in 2007 at City Hospital Birmingham, to investigate patients with suspected hypersensitivity reactions to anaesthetic drugs from hospitals mainly within the West Midlands. Both the British Society for Allergy and Clinical Immunology (BSACI) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) recommend the involvement of both an anaesthetist and an allergist in these clinics, as the identification of the nature of the reaction and causative agents is often complex in the context of the peri-operative setting [1, 2].

The referral of patients with suspected hypersensitivity reactions to anaesthetic drugs for further investigations is now considered mandatory, and is the responsibility of the primary anaesthetist involved [2–4]. A study from 2005 showed that an informed guess was not a reliable way of determining the cause of a suspected hypersensitivity reaction during anaesthesia, and may put a significant number of patients at unnecessary risk [5]. The aims of our service were: to determine the cause of the event; to identify any agent responsible; to determine those drugs which were safe to use in future anaesthetics; and to make recommendations

for safe peri-operative care. We report the results of a seven-year review of patients referred to our bi-specialty clinic with suspected hypersensitivity reactions during anaesthesia.

The European Academy for Allergology and Clinical Immunology revised the nomenclature in 2004 [6], and recommended that the term hypersensitivity be used for objectively reproducible symptoms or signs initiated by exposure to a defined stimulus, at a dose tolerated by normal persons. Following investigation, diagnosis should then be broken down into IgE-mediated and non-IgE-mediated hypersensitivity. The term anaphylaxis should be used for all severe, life-threatening hypersensitivity reactions, whether these were IgE or non-IgE-mediated reactions. This terminology is used throughout.

We wished examine the nature and patterns of suspected hypersensitivity reactions associated with anaesthesia referred to a regional specialist centre in the UK, and to identify and describe the pathophysiological causes of these reactions, adding to the existing evidence base. We also sought to compare this UK-derived data to the experience reported in other European countries and Australia.

Methods

We created a database following approval from our hospital's Clinical Effectiveness department, and stored in accordance with the hospital's information governance protocols.

Patients were generally referred to this clinic for further investigations either because they had experienced a suspected hypersensitivity reaction associated with a recent anaesthetic, or because the patient was awaiting surgery, but had reported a past history of previous uninvestigated reaction(s) associated with anaesthesia.

The approach to the investigation of suspected hypersensitivity reactions in our bi-specialty clinic is detailed below.

The history from the referring clinician was reviewed, together with any details the patient may have recalled. We paid particular attention to past history of anaesthetic exposure, any known drug allergies, a history of other reactions, including spontaneous (idiopathic) urticaria or angioedema, and a history of

other allergic diseases or asthma. We then examined the anaesthetic chart to confirm the drugs or agents administered, and the timing of administration in relation to the reported clinical features.

When available, serum tryptase levels taken peri-operatively were used in the assessment. Tryptase elevation is an indicator of mast cell activation in systemic anaphylaxis, or mastocytosis [7]. A serum tryptase level greater than $14 \mu\text{g.L}^{-1}$ [8] or a 100% increase in two serial tryptase samples taken during the reaction, was interpreted as significant. When no baseline tryptase was available, we took samples during the clinic attendance for analysis (Unicap 250; Thermo Fisher Scientific, Uppsala, Sweden), since baseline samples can be taken at any time point 24 h after the reported reaction. However, samples taken and their timing were entirely dependent on the anaesthetist managing the patient at the time, and hence there was some variation in practice.

The first line investigation in the clinic was to skin prick test the patient with the drugs/agents administered before the reaction. We performed skin prick tests at therapeutic concentration or known non-irritant concentration based on the information available (EAACI guidelines 2005, BSACI guidelines 2009, ENDA guidance 2013) [1, 9, 10]. When applicable, in positive cases, alternative drugs from the same class (e.g. neuromuscular blocking drugs) were tested to provide safe alternatives for future anaesthetics [11].

When no response was observed on skin prick testing to a drug strongly suspected of causing the reaction, we performed intradermal testing at a recommended dilution.

Serum-specific IgE assays to the possible causal agent were performed where available, using Phadia Immucap[®] (Thermo Fisher). Assays available to our clinic included: latex; chlorhexidine; suxamethonium; penicillins; gentamicin; gelofusine; lignocaine; and morphine.

We reached a diagnosis following review of the history, anaesthetic records, and investigations undertaken, including serum tryptase. A positive skin test and/or a positive serum-specific IgE assay result was regarded as confirmatory of IgE-mediated hypersensitivity. Limitations of skin tests and serum-specific IgE testing are well recognised [1]. False positive skin tests

due to direct histamine-releasing effects of some drugs are well known. Serum-specific IgE assays to agents other than latex have not been fully validated. While recognising these limitations, we interpreted positive skin tests and/or serum-specific IgE as confirming IgE-mediated hypersensitivity where this was in keeping with the overall clinical picture.

Some drugs are known to cause histamine release and a raised tryptase level without an IgE-mediated mechanism, for example vancomycin. However, there was no effective way of differentiating IgE-mediated reactions from direct histamine release with these drugs. With these limitations in mind, where the reaction had been severe with positive skin prick testing, we made a diagnosis of an IgE-mediated reaction, and advised future avoidance of the drug.

In patients suspected of having a hypersensitivity reaction, we graded the severity of the reaction according to the adapted Ring and Messmer's [12, 13] grading system for generalised hypersensitivity reactions:

Grade 1 – cutaneous or mucous signs only: mild.

Grade 2 – moderate multi-visceral signs: measurable, but not life-threatening cardiovascular (tachycardia, hypotension), gastrointestinal (nausea) or respiratory disturbance.

Grade 3 – life-threatening mono- or multi-visceral signs: cardiovascular collapse, and/or cardiac dysrhythmias, and/or bronchospasm, and/or mucocutaneous or gastrointestinal symptoms.

Grade 4 – cardiac and/or respiratory arrest.

We included all patients who attended the joint specialty clinic from September 2007 to December 2014 in the sample. The items of patient information recorded in the database included: age; sex; date of clinic attendance; history of atopy and allergy; the operation details; clinical presentation and grade of severity of the reaction; management of the reaction and consequences; serum tryptase and IgE assay results; suspected causal agent; skin test positive agent; and final diagnosis.

We analysed patient data in two groups: those seen after a recent suspected hypersensitivity reaction during an operation (the 'postoperative' group); and those awaiting an operation, but with an uncertain past history of previous hypersensitivity reaction to

anaesthetics (the 'pre-operative' group). This division was warranted, as the clinical history and features of the reaction during an anaesthetic in the 'pre-operative' group were self-reported. The patients in the 'postoperative' group were usually referred by a senior anaesthetist following a recent suspected reaction. The details included a full list of the drugs administered, contemporaneous observations, full description of the clinical features, treatment measures and any follow-up investigations completed, e.g. serum tryptase measurements.

We performed data analysis with Pivot tables in Microsoft Excel, and calculated percentages. We compared a previous history of allergy or atopy with diagnosis of IgE-mediated hypersensitivity using contingency tables and two-tailed Fisher's exact testing. A *p* value of < 0.05 was considered significant. Statistical analyses were performed using Prism version 6.0 (Graphical software, San Diego, CA, USA).

Results

We assessed 410 patients in our clinic, (117 male subjects (29%), 293 female subjects) median (IQR [range]) age 48 (32–63 [1–87]) years. The results were analysed and presented in two cohorts: the 'postoperative' group and the 'pre-operative' group.

Postoperative group (n = 316)

IgE-mediated hypersensitivity reactions

Of the 316 patients in the postoperative group, 173 (54.7%) patients were diagnosed as having had an IgE-mediated hypersensitivity reaction (114, 66% female subjects and 59, 34% male subjects). Table 1 provides a full list of the agents identified.

Of the 173 IgE-mediated reactions, 15 (8.9%) patients had grade 4 reactions (cardiac arrest), 99 patients (58.6%) suffered grade 3 reactions, 39 (23.0%) were grade 2 and 16 (9.5%) were grade 1. The severity was unclear from the history in four cases. All 12 reactions to patent blue dye were grade 3 reactions. For all other agents, the spread of severity of reactions closely mirrored the above trend.

Table 2 summarises the clinical features of the reactions experienced by patients, categorised as cardiovascular, respiratory, mucocutaneous and gastrointestinal. The predominant feature in the IgE-mediated

ated hypersensitivity reaction group was cardiovascular involvement (132 patients, 78.1%), of whom 15 (8.8%) suffered cardiac arrest.

In the IgE-mediated hypersensitivity reaction group, the cardiovascular or the mucocutaneous systems were the only systems evidently affected according to the referral information in 12 (7.1%) and 22 (13.0%) patients, respectively.

IgE assays were taken in 128 (40.5%) patients in the postoperative cohort. In 77 of these cases, a diagnosis of IgE-mediated hypersensitivity reaction was made on the basis of skin tests. Twenty-six of these 77

patients had a positive IgE assay contributing to a diagnosis of IgE-mediated hypersensitivity reaction. The results of the IgE assays are summarised in Table 3.

The referring clinician suggested a suspected causal drug in 153 (48.4%) of the 316 postoperative cases. The suspected drug was confirmed as the causative agent for IgE-mediated hypersensitivity reaction in only 57 (37.2%) patients.

Non-IgE-mediated hypersensitivity reactions

In 89 patients (28.1%), a diagnosis of non-IgE-mediated hypersensitivity reaction was made. These were largely patients who had a prior history of spontaneous (idiopathic) urticaria and/or angioedema, where clinical evaluation was in keeping with acute urticaria during anaesthesia, precipitated by recognised triggers such as stress and infection [14]. This group also included patients with angioedema secondary to angiotensin-converting enzyme inhibitors. We diagnosed mastocytosis in two patients (2.4%) where there were typical clinical features and a persistently raised level of mast cell tryptase.

In comparison with the IgE-mediated hypersensitivity reactions, most reactions in the non-IgE-mediated group were grade 1 ($n = 43$, 50%). A further 22 (25.5%) were grade 2, 20 (23.3%) grade 3 and one (1.2%) grade 4. The clinical features are illustrated in Table 2. The predominant feature in the non-IgE hypersensitivity reaction group was mucocutaneous involvement ($n = 72$, 83.7%). Only 27 (31.4%) of these patients had included cardiovascular features, of whom one (1.2%) suffered cardiac arrest (secondary to hypoxia thought to be related to difficult tracheal intubation, rather than the cardiovascular effects of the non-IgE-mediated reaction). The cardiovascular system or the mucocutaneous system was the sole organ system affected in 6 (7.0%) and 49 (57.0%) patients, respectively.

Of the 316 subjects reviewed postoperatively, serum tryptase samples had been taken at the referral hospital in 173 patients (54.7%). In 37 (21.3%) patients, samples were either not reported at all, partially reported, not timed or lost. Of the 173 patients with IgE-mediated reactions, serum tryptase samples were taken at the time of the reaction in 127

Table 1 Agents responsible for IgE-mediated hypersensitivity reactions. Values are number (proportion).

	Postoperative group (n = 173)	Pre-operative group (n = 29)
Neuromuscular blocking drugs	65 (37.6%)	17 (58.6%)
Atracurium	23 (35.4%)	8 (47.1%)
Rocuronium	20 (30.8%)	2 (11.8%)
Suxamethonium	12 (18.5%)	6 (35.3%)
Vecuronium	8 (12.3%)	1 (5.9%)
Cis-atracurium	1 (1.5%)	0
Pancuronium	1 (1.5%)	0
Antibiotics	54 (31.2%)	3 (10.3%)
Penicillin	40 (74.1%)	1 (33.3%)
Gentamicin	6 (11.1%)	1 (33.3%)
Cefuroxime	1 (1.9%)	1 (33.3%)
Ciprofloxacin	2 (3.7%)	0
Metronidazole	1 (1.9%)	0
Vancomycin	1 (1.9%)	0
Teicoplanin	3 (5.6%)	0
Chlorhexidine	15 (8.7%)	1 (3.4%)
Patent blue dye	12 (6.9%)	0
Latex	10 (5.8%)	0
Opioids	3 (1.7%)	0
Fentanyl	2 (66.7%)	0
Morphine	1 (33.3%)	0
Local anaesthetics	3 (1.7%)	3 (10.3%)
Lignocaine	2 (66.7%)	1 (33.3%)
Bupivacaine	1 (33.3%)	0
Prilocaine	0	1 (33.3%)
Mepivacaine	0	1 (33.3%)
Gelofusine	3 (1.7%)	0
Propofol	2 (1.2%)	2 (6.8%)
Steroids or excipients (e.g. Carboxymethylcellulose)	3 (1.7%)	0
Niopam	1 (0.6%)	0
Ondansetron	1 (0.6%)	1 (3.4%)
NSAID	0	1 (3.4%)
Paracetamol	0	1 (3.4%)
Ranitidine	1 (0.6%)	0

NSAID, non-steroidal anti-inflammatory drugs.

Table 2 Organ systems affected. There were four cases in the IgE hypersensitivity group and three in the non-hypersensitivity adverse reaction group where the nature of the reaction was unclear from the history. Values are number (proportion).

Organ system	IgE hypersensitivity (n = 169)	Non-IgE hypersensitivity (n = 86)	Non-hypersensitivity adverse reaction (n = 54)
CVS	132 (78.1%)	27 (31.4%)	33 (61.1%)
RS	89 (52.7%)	23 (26.7%)	16 (29.6%)
MC	106 (62.7%)	72 (83.7%)	30 (55.5%)
GIT	6 (3.6%)	6 (7.0%)	8 (14.8%)

CVS, cardiovascular (hypotension, tachycardia, arrhythmias); RS, respiratory system (bronchospasm, desaturation); MC, mucocutaneous (urticarial, erythema, angioedema); GIT, gastrointestinal system (abdominal pain, diarrhoea, vomiting).

Table 3 IgE assays performed as part of the diagnostic work-up and their results. Values are number (proportion).

	Total number of assays requested	Positive assays
Amoxicillin	19	6 (31.6%)
Other penicillins	40	5 (12.5%)
Latex	54	3 (5.6%)
Chlorhexidine	51	9 (17.6%)
Suxamethonium	25	3 (12%)
Morphine	19	4 (21.1%)
Gelofusine	1	1 (100%)
Gentamicin	2	1 (50%)
Pholcodine	1	1 (100%)
Lignocaine	14	0
Bupivacaine	4	0
Mepivacaine	2	1 (50%)
Prilocaine	1	1 (100%)
Acetylsalicylic acid	1	0
Rocuronium	1	0
Clavulanic acid	2	0
Ciprofloxacin	1	0
Metronidazole	1	0
Diclofenac	1	0

patients (73.4%), assisting in diagnosis. Serum tryptase concentrations were elevated above the upper limit of our reference range ($14 \mu\text{g.l}^{-1}$) in 57 patients (44.9%) in the IgE-mediated hypersensitivity group. Serum tryptase concentrations were not elevated in any patient tested in the non-IgE-mediated group (excluding the two patients with mastocytosis).

Non-hypersensitivity adverse reactions

In the remaining 54 patients (17%), the adverse reactions were not considered to be hypersensitivity reactions, but rather recognised side effects of the anaesthetic agent

and/or technique. Four of these patients suffered cardiac arrest, for reasons other than a hypersensitivity anaphylactic reaction. For example, one patient had a cardiac arrest probably precipitated by prolonged QT-interval following intravenous ondansetron.

Pre-operative group (n = 94)

A diagnosis of IgE-mediated hypersensitivity reaction, based on the clinical history given and confirmed by skin prick/intradermal testing or IgE assays was made in 29 (30.8%) patients (Table 1). In another 30 (31.9%) patients, a diagnosis of a non-IgE-mediated hypersensitivity reaction was made. The adverse reaction was not considered to be a hypersensitivity reaction in the remaining 35 (37.2%) patients.

IgE assays were taken in 25 patients, and were found to be positive in four patients. In one patient, the serum-specific IgE assay was weakly positive to mepivacaine and prilocaine, but an IgE-mediated hypersensitivity reaction was excluded on challenge testing, indicating that the IgE assay was a false positive.

Of the 82 patients diagnosed with IgE-mediated hypersensitivity reactions to neuromuscular blocking drugs from both cohorts, 23 (28%) also demonstrated cross-reactivity to other neuromuscular blocking drugs tested.

Both cohorts of pre-operative and postoperative patients with diagnoses of IgE-mediated hypersensitivity reactions were less likely to have a history of atopy and/or allergy (n = 71, 35.4%) compared with those with a diagnosis of non-IgE-mediated hypersensitivity reaction (n = 78, 65.8%) (p = 0.0001, OR 0.285, 95% CI 0.177–0.459). Patients diagnosed with latex IgE-mediated reac-

tions were most likely to give a positive history of atopy or allergy (10/10 cases; 100%).

Discussion

In our postoperative cohort of patients, the commonest causes of IgE-mediated hypersensitivity reactions were neuromuscular blocking drugs (37.6%), antibiotics (31.2%), chlorhexidine (8.7%), patent blue dye (6.9%) and latex (5.8%). In the largest series of anaesthesia-associated IgE-mediated hypersensitivity reactions published (from France), the commonest culprit agents were neuromuscular blocking drugs (47.4%), latex (20%), antibiotics (18.1%) and dyes (4.4%) [15]. In France, there is a well-established network of clinics (GERAP) dedicated to the investigation of peri-operative anaphylaxis using a standardised protocol [16].

Both our study and the above French study (Dong et al.) showed that although neuromuscular blocking drugs were still the major cause of IgE-mediated reactions, they accounted for a lower proportion of cases from 1993 to 2012 [15–19]. This trend is similar to that reported by investigators in Australia, who found that neuromuscular blocking drugs accounted for 38% of cases [20]. In comparison, published data from a single centre in Norway showed a high proportion of IgE-mediated reactions to neuromuscular blocking drugs (93.2%) [21]. This difference could be explained by referral bias, genetically based differences, differences in anaesthetic practice (e.g. reduced usage of neuromuscular blocking drugs, increased regional anaesthetic techniques etc.), and differences in exposure to different neuromuscular blocking drugs or other sensitising agents. An example of the former is wide exposure to rocuronium [22]. An increased risk of reaction to rocuronium has been recognised in France [17] and also recently in Australia [23]. IgE-mediated anaphylaxis to neuromuscular blocking drugs is often seen with the first clinical exposure indicating prior sensitisation. Sensitising agents containing a substituted ammonium group have been implicated [24, 25]. These compounds occur widely in the environment in cosmetics, disinfectants, industrial materials and foods. Drugs have also been postulated as another source of sensitisation, especially pholcodine, although that association has been questioned, given the general population exposure to the agent both in

France and the UK [26]. In addition, a review by the European Medicines Agency [27] concluded that the existing evidence does not support the conclusion that the use of pholcodine-containing medicines presents a risk of developing anaphylactic reactions to neuromuscular blocking agents. This does not rule out the possibility of other substituted ammonium compounds being a source of sensitisation.

Antibiotics accounted for a high proportion (31.2%) of reactions in our postoperative group, and this may have accounted for the lower proportion due to neuromuscular blocking drugs in our cohort. Data from Spain showed that the commonest causative agents of IgE-mediated hypersensitivity reactions during anaesthesia were antibiotics (44%) [28]. The incidence of anaesthesia-associated hypersensitivity reactions due to antibiotics appears to be increasing (personal observation of the authors). This could be due to increasing exposure to antibiotics within the community, and/or to altered practice with regard to peri-operative antibiotic usage.

We found latex accounted for only 5.8% of all anaesthesia-associated reactions, with no cases diagnosed in the last two years. This decreasing trend has also been noted in other studies [15, 29]. This is commonly thought to be due to the use of powder-free and low-allergen latex gloves [30], and to the decreasing use of latex products in general, leading to decreased sensitisation.

Of interest is the relatively higher proportion of cases due to patent blue dye (6.9%). This finding is also in keeping with the observation from another single centre in the UK [31]. Previously, the incidence of anaphylaxis to patent blue dye was reported to be just 0.4% [32]. All 12 reactions to patent blue in our series were classed as severe reactions (grade 3), with hypotension being a prominent feature in all cases. This emphasises the importance of the warning from the European Medicines Agency [33] that healthcare professionals need to be made aware of the risk of anaphylactic reactions whenever these agents are used [34].

Chlorhexidine accounted for 8.7% of IgE-mediated hypersensitivity reactions. A publication from Denmark reported a higher incidence of 11% [35]. The differences in identification of chlorhexidine

allergy may be dependent on the practice of routine testing for chlorhexidine allergy in patients suspected of peri-operative hypersensitivity and anaphylactic reactions.

Fisher studied the benefits of pre-operative detection of the risk of anaphylaxis during anaesthesia in a group of 144 patients in 2007 [36]. The only at-risk group that could be identified were patients with a history of an unexplained severe adverse reaction during a previous anaesthetic. Twenty-two of 45 patients (49%) with such a history had positive skin tests to an anaesthetic drug. He concluded that patients with a history of a severe undiagnosed adverse event during previous anaesthesia should be investigated before undergoing further elective surgery. In our cohort of 'pre-operative' patients, 29 (30.8%) had a diagnosis of IgE-mediated hypersensitivity reactions, lending weight to this argument. Further support for investigating unexplained peri-operative adverse reactions comes from the study by Malinovsky et al. [37], who also demonstrated that a systematic approach to investigating such reactions identified the culprit agent in a significant number of cases.

All ten of our patients diagnosed with latex allergy had a positive history of atopy and/or allergy. These findings are consistent with those reported by others [17, 38].

In contrast, there was no correlation between a prior history of atopy or allergy and a diagnosis of IgE-mediated hypersensitivity for all the other causative agents. It is well recognised that susceptibility to IgE-mediated hypersensitivity to drugs is not dependent on any prior history of allergy [39], and the only known risk factor for peri-operative IgE-mediated hypersensitivity reaction is a previous immediate anaesthesia-associated reaction that was not investigated.

Only 28% of our patients diagnosed with IgE-mediated hypersensitivity reactions to a neuromuscular blocking agent exhibited cross-reactivity to other neuromuscular blocking agents on skin testing. This is not as high as previously reported figures of cross-reactivity, which reported it in at least 60% of cases [18, 23, 40]. However, our data should be interpreted with caution, as our lower incidence of cross-reactivity may be explained by our practice of testing against a limited range of agents used commonly in the UK.

It is important for anaesthetists to remember that the presentation of IgE-mediated hypersensitivity reaction may involve only one organ system [17]. Although the system most commonly affected in IgE-mediated hypersensitivity reactions was the cardiovascular system (78.1%, Table 2), we identified IgE hypersensitivity in 23 (13.2%) patients with isolated mucocutaneous reactions. We recommend that all patients with suspected peri-operative hypersensitivity reactions, including those who only experienced isolated mucocutaneous reactions, are referred for further investigation in a specialist clinic.

Elevated serum tryptase is a strong indication that an IgE-mediated hypersensitivity reaction has occurred. In one study, the positive predictive value of tryptase for the diagnosis of IgE-mediated reactions during anaesthesia was 93% [17]. Only 173 (54.7%) patients with suspected hypersensitivity reaction referred to our clinic had bloods taken for serum tryptase measurement. An important message to clinicians who refer patients with suspected hypersensitivity reactions is to ensure blood samples are taken for serum tryptase analysis according to recommended time intervals [1–4]. Indeed, a recent editorial suggested that even more samples should be taken, for example at one, two, three, six, 12 and 24 hours after a reaction, to ensure that at least some of these samples reach the laboratory and demonstrate the rise and fall of serum tryptase concentrations [41].

Serum-specific IgE testing alone is of limited benefit in the investigation of drug allergy [42], due to the limited number of tests available, and to the low sensitivity. Morphine IgE assay has been used to identify neuromuscular blocking drug sensitivity. In keeping with this, we detected morphine specific IgE in patients with neuromuscular blocking drug sensitivity. We also detected morphine specific IgE in a patient with suspected morphine allergy. It is not known if there is a difference in the epitopes recognised.

Serum-specific IgE results may be false positives; drugs such as local anaesthetics may be further investigated through challenge testing, but clearly this approach is not feasible with most intravenous anaesthetic agents. Where it is not possible to determine that a serum-specific IgE result is a false positive, we recommended future avoidance of the drug. The

majority of serum-specific IgE assays in our cohorts of patients were negative, in keeping with the known low sensitivity of these investigations.

The suspected causal drug stated by the referring clinician was only proven to be implicated in 37.2% of cases. This reinforces the message conveyed by Kroigaard and colleagues in 2005 [5], who said that an informed guess is not a reliable way of determining the cause of a suspected hypersensitivity reaction, a fact compounded by the high number of different drugs administered in a short period of time during anaesthesia. It is also worrying that 10% of anaesthesia-related immediate hypersensitivity reactions reported to the UK Medicines Control Agency were fatal [43]. Therefore, it is essential that patients with suspected hypersensitivity reactions during anaesthesia are referred for further investigations to confirm the cause of the reaction, so that they are not put at risk of subsequent re-exposure to the real allergen.

In view of the complexity of suspected anaesthesia-associated hypersensitivity reactions, it is essential to follow a systematic approach when investigating these reactions. This should be complemented by clinicians taking appropriately-timed samples for tryptase measurement, and direct referral to a specialist centre. As the clinical presentation of both IgE-mediated and non-IgE-mediated reactions can be very similar, even those patients presenting with isolated mucocutaneous features should be fully investigated.

We have identified the current pattern of agents responsible for anaesthesia-associated hypersensitivity reactions in the UK. Knowledge of the common causative agents should guide appropriate approaches to investigating patients who experience unexplained peri-operative adverse reactions. In addition, this information may raise awareness of potential allergens in the peri-operative setting [29].

Competing interests

No external funding and no competing interests declared.

References

1. Ewan PW, Dugue P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines for the investigation of suspected ana-

- phylaxis during general anaesthesia. *Clinical and Experimental Allergy* 2009; **40**: 15–31.
2. Harper NJN, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211.
3. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anaesthesia: 2011 updated guidelines for clinical practice. *Journal of Investigative Allergology and Clinical Immunology* 2011; **21**: 442–53.
4. Kroigaard M, Garvey LH, Gillberg SG, et al. Scandinavian Clinical Practice Guidelines on the diagnosis and follow up of anaphylaxis during anaesthesia. *Acta Anaesthesiologica Scandinavica* 2007; **51**: 655–70.
5. Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *British Journal of Anaesthesia* 2005; **95**: 468–71.
6. Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the nomenclature review committee of the World Allergy Organization, October 2003. *Journal of Allergy and Clinical Immunology* 2004; **113**: 832–6.
7. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *New England Journal of Medicine* 1987; **316**: 1622–6.
8. Ward M, Sheldon J, Rowbottom A, Wild GD. *PRU Handbook of Clinical Immunochemistry*, 9th edn. Sheffield: PRU Publications, 2007.
9. Mertes PM, Laxenaire MC, Lienhart A, et al. Working Groups of SFAR, ENDA and EEACI. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *Journal of Investigative Allergology and Clinical Immunology* 2005; **15**: 91–101.
10. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs – an ENDA/EACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12.
11. Ramirez LF, Pereira A, Chiriac AM, Bonnett-Boyer MC, Demoly P. Negative predictive value of skin tests to neuromuscular blocking agents. *Allergy* 2012; **67**: 439–41.
12. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **1**: 466–9.
13. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anaesthesia: controversies and new insights. *Anesthesiology* 2009; **111**: 1141–50.
14. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angioedema. *Clinical and Experimental Allergy* 2007; **37**: 631–50.
15. Dong SW, Mertes PM, Petitpain N, et al. GERAP. Hypersensitivity reactions during anaesthesia. Results from the ninth French survey (2005–2007). *Minerva Anesthesiologica* 2012; **78**: 868–78.
16. Laxenaire MC. Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicenter epidemiological inquiry. *Annals Françaises d'Anesthésie et de Réanimation* 1993; **12**: 91–6.
17. Mertes PM, Laxenaire MC, Alla F. Groupe d'Etudes des Réactions Anaphylactiques. Anaphylactic anaphylactoid reactions occurring during anaesthesia in France in 1999–2000. *Anesthesiology* 2003; **99**: 536–45.
18. Laxenaire MC, Mertes PM. Grouped Etudes des Reactions Anaphylactiques. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *British Journal of Anaesthesia* 2001; **87**: 549–58.

19. Mertes PM, Alla F, Trechot P, et al. Anaphylaxis during anaesthesia in France: an 8-year national survey. *Journal of Allergy and Clinical Immunology* 2011; **128**: 366–73.
20. McNeill O, Kerridge RK, Boyle MJ. Review of procedures for investigation of anaesthesia-associated anaphylaxis in Newcastle, Australia. *Anaesthesia and Intensive Care* 2008; **36**: 201–7.
21. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anaesthesia in Norway: a 6-year single center follow-up study. *Anesthesiology* 2005; **102**: 897–903.
22. Guttormsen AB. Allergic reactions during anaesthesia – increased attention to the problem in Denmark and Norway. *Acta Anaesthesiologica Scandinavica* 2001; **45**: 1189–90.
23. Sadleir PHM, Clarke RC, Bunning DL, et al. Anaphylaxis to neuromuscular blocking drugs: incidence and cross reactivity in Western Australia 2002–2011. *British Journal of Anaesthesia* 2013; **110**: 981–7.
24. Payne V, Kam PCA. Mast cell tryptase: a review of its physiology and clinical significance. *Anaesthesia* 2004; **59**: 695–703.
25. Baldo BA, Fisher MM, Pham NH. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. *Clinical and Experimental Allergy* 2009; **39**: 325–44.
26. Johansson SG, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE sensitisation: a multicentre study. *Allergy* 2010; **65**: 498–502.
27. European Medicines Agency. Questions and answers on the review of the marketing authorisations for medicines containing pholcodine. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pholcodine_31/WC500117795.pdf (accessed 15/07/2014).
28. Lobera T, Audicana MT, Pozo MD, et al. Study of hypersensitivity reaction and anaphylaxis during anaesthesia in Spain. *Journal of Investigative Allergology and Clinical Immunology* 2008; **18**: 350–6.
29. Carle C, Harper NJN. Anaphylactic reactions associated with anaesthesia. *Anaesthesia and Intensive Care Medicine* 2010; **11**: 391–3.
30. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *Journal of Allergy and Clinical Immunology* 2010; **126**: e1–42.
31. Robinson L. Anaphylaxis to dye during breast surgery. *Anaesthesia* 2011; **66**: 841–2.
32. Hunting AS, Nopp A, Johansson SGO, Andersen F, Wilhelmsen V, Guttormsen AB. Anaphylaxis to Patent Blue V. I. Clinical aspects. *Allergy* 2010; **65**: 117–23.
33. European Medicines Agency. Blue dyes (e.g. Patent Blue V, Sulphan Blue) – risk of serious allergic reactions. In: *PhVWP Monthly Report on Safety Concerns, Guidelines and General Matters*. 2012. Issue number: 1204. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/04/WC500126250.pdf (accessed 15/07/2014).
34. Haque RA, Wagner A, Whisken JA, Nasser SM, Ewan PW. Anaphylaxis to patent blue V: a case series and proposed diagnostic protocol. *Allergy* 2010; **65**: 396–400.
35. Garvey LH, Roed-Petersen J, Menne T, Husum B. Danish Anaesthesia Allergy Centre – preliminary results. *Acta Anaesthesiologica Scandinavica* 2001; **45**: 1204–9.
36. Fisher M. The preoperative detection of risk of anaphylaxis during anaesthesia. *Anaesthesia and Intensive Care* 2007; **35**: 899–902.
37. Malinowski JM, Decagny S, Wessel F, Guilloux L, Mertes PM. Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. *Acta Anaesthesiologica Scandinavica*. 2008; **52**: 175–81.
38. Demaegd J, Soetens F, Herregods L. Latex allergy: a challenge for anesthetists. *Acta Anaesthesiologica Belgica* 2006; **57**: 127–35.
39. Fisher M, Outhred A, Bowey CJ. Can clinical anaphylaxis to anaesthetic drugs be predicted from allergic history? *British Journal of Anaesthesia* 1987; **59**: 690–2.
40. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; **62**: 471–87.
41. Sheldon J, Philips B. Laboratory investigation of anaphylaxis: not as easy as it seems. *Anaesthesia* 2015; **70**: 1–5.
42. Dewachter P, Mouton-Faivre C. What investigation after an anaphylactic reaction during anaesthesia? *Current Opinion in Anaesthesiology* 2008; **21**: 363–8.
43. AAGBI Guidelines. *Suspected Anaphylactic Reactions Associated with Anaesthesia*. London: The Association of Anaesthetists of Great Britain and Ireland and British Society of Allergy and Clinical Immunology, 2003.