Anaphylaxis during general anaesthesia: experience from a drug allergy centre in the UK

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Editorial Comment
A large city drug allergy testing centre reports here on a cohort over several years tested for suspected allergic reaction during general anaesthesia. A severe reaction (by history) and actual drug allergy was identified for the majority, but not for all. Mostly, these were antibiotics and neuromuscular relaxants.

Anaphylaxis during general anaesthesia (GA) is rare but can be severe, as it is often complicated by significant morbidity. Epidemiological studies conducted in France reported the incidence of anaphylaxis during GA as 1 in 13,0001–3 whereas in Australia, the reported incidence ranges from 1 in 10,000 to 1 in 20,000.4 Although mortality from perioperative anaphylaxis has been previously quoted as between 3–9%,5 a more recent study put it in the range of 0–1.4%.6

Identification of the cause of anaphylaxis may pose a significant dilemma to the allergist and anaesthetist. The allergic reaction mechanisms of many drugs are not known, and validated test protocols are lacking. Therefore, clinical judgement is essential in the interpretation of the...
investigation results, and any conclusions reached must be compatible with the patient’s clinical history (anaesthetic chart) and depend on the experience of the allergist to a large extent. In this study, we describe our experience in the investigation of anaphylaxis under GA and compare data from our centre with those from other series.

Methods

All patients who attended the Drug Allergy Unit at University College London Hospital between March 2013 and Dec 2015 with suspected perioperative anaphylaxis during GA were reviewed retrospectively from hospital notes and electronic records. Patients who met one or more of the following conditions were excluded: (1) reactions with local or regional anaesthesia; (2) referrals for predictive tests for future use of anaesthetic agents for patients with a history of multiple drug allergies but without prior history of adverse reactions during anaesthesia; (3) referrals for identification of safe drugs and agents for future use in GA because the patient had an adverse reaction during prior GA, but the reaction was in the distant past and not clearly documented and (4) incomplete assessment or loss to follow-up.

Clinical history

The clinical histories were evaluated systematically based on information provided by the patients, referral letters from the surgeons or anaesthetists and the anaesthetic charts. When further information was required, the referring anaesthetist was contacted. The anaesthetic and drug charts were carefully scrutinised to assess the clinical features and determine the temporal association of events with drug administration. This assessment enabled the preparation of a list of possible culprits (all drugs and agents used during perioperative period with clear temporal association with anaphylaxis).

The severity of the perioperative allergic reactions was graded according to Ring and Messmer system: I Cutaneous signs: generalised erythema, urticaria, angioedema; II Measurable but not life-threatening symptoms: Cutaneous signs, hypotension, tachycardia Respiratory disturbances: cough, difficulty inflating; III Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm; IV Cardiac and/or respiratory arrest.5

Whenever available, serum tryptase levels, obtained at the time of the anaphylaxis were reviewed. An elevated serum tryptase level was defined as higher than 14 μg/l, based on the normal laboratory values (2–14 μg/l).

Skin testing in allergological evaluation

All potential culprits were tested; however, the order of the testing was adapted according to the clinical history of each patient and the timing of the onset of the reaction in relation to the introduction of the drug.

General anaesthetics

The concentrations of general anaesthetics used for skin testing are summarised in Table 1. The procedure for skin testing followed the general principles laid out in the British Society for Allergy and Clinical Immunology (BSACI) drug allergy guideline.7 SPT was performed on the volar forearm and read after 15–20 min. A weal diameter at least 3 mm larger than that of the negative control was considered positive. The coexistence of flare and itch supported a positive result.8–10 When SPT was negative or indeterminate, an intradermal test (IDT) was performed. 0.02–0.03 ml of dilutions of commercial preparations was injected into the dermis of the volar forearm to produce an injection papule no larger than 4 mm in diameter. The result was read after 15–20 min. An increase in weal size of more than 3 mm from the initial papule with accompanying flare was considered positive.10 When skin testing was positive for a specific neuromuscular blocking agent (N MBA), cross-sensitisation workup was performed with the remaining NMBAs.

Antibiotics

Whenever GA involved penicillins, investigations for penicillin allergy were performed. Briefly, all penicillin determinants were evaluated: penicilloyl poly-L-lysine (PPL), minor determinant mixture (MDM), benzylpenicillin...
Clavulanic acid and flucloxacillin were selected if they were indicated as the culprit drugs. The concentrations of agents for skin testing are summarised in Table 2. Serum-specific IgE (sIgE) testing was performed for penicillin V, penicillin G and amoxicilloyl (Phadia, Uppsala, Sweden). If skin testing and sIgE were negative, a supervised oral challenge was performed. A positive result for penicillin was followed by cefuroxime testing to determine future use.

If a cephalosporin was suspected as the cause, the index cephalosporin was evaluated alongside penicillin allergy determinants; if both were negative, challenge with cephalosporin was performed. For non-ß-lactam antibiotics, there are less data on the sensitivity and specificity of the test, and a sequential testing approach was used: SPT (neat), IDT (1 : 100, 1 : 10), and then oral challenge were considered. Because gentamicin has been found to be irritant in skin testing, this test was not performed, and patients were challenged intravenously if necessary.

Table 1: Concentrations of anaesthetic drugs used in skin testing.

| Drug           | Concentration | Skin prick test | Intradermal test |
|----------------|---------------|-----------------|------------------|
| **NMBAs**      |               |                 |                  |
| Suxamethonium  | 50 mg/ml      | 1 : 5           | 1 : 50,000       | 1 : 500          | /                |
| Rocuronium     | 10 mg/ml      | 1 : 2           | 1 : 20,000       | 1 : 200          | /                |
| Vecuronium     | 4 mg/ml       | 1 : 10          | 1 : 10,000       | 1 : 100          | 1 : 10           |
| Mivacurium     | 2 mg/ml       | 1 : 2           | 1 : 10,000       | 1 : 100          | /                |
| Atracurium     | 10 mg/ml      | 1 : 10          | 1 : 10,000       | 1 : 100          | /                |
| Pancuronium    | 2 mg/ml       | 1 : 10          | 1 : 10,000       | 1 : 100          | /                |
| **Hypnotics**  |               |                 |                  |
| Thiopental     | 25 mg/ml      | 1 : 10          | /                | 1 : 1000         | 1 : 100          | /                |
| Midazolam      | 5 mg/ml       | 1 : 10          | /                | /                | 1 : 10           |
| Ketamine       | 10 mg/ml      | 1 : 10          | /                | 1 : 1000         | 1 : 100          | 1 : 10           |
| Propofol       | 10 mg/ml      | 1 : 10          | /                | 1 : 1000         | 1 : 100          | 1 : 10           |
| **Opioids**    |               |                 |                  |
| Fentanyl       | 0.05 mg/ml    | Neat            | /                | 1 : 1000         | 1 : 100          | 1 : 10           |
| Alfentanly     | 0.5 mg/ml     | Neat            | /                | 1 : 1000         | 1 : 100          | 1 : 10           |
| Remifentanly   | 0.05 mg/ml    | Neat            | /                | 1 : 1000         | 1 : 100          | 1 : 10           |
| **Local anaesthetics** |   |                 |                  |
| Bupivacaine    | Neat          | /               | /                | /                | 1 : 10           |
| Lidocaine      | Neat          | /               | /                | /                | 1 : 10           |
| **Others**     |               |                 |                  |
| Gelofusine     | 4%            | Neat            | /                | 1 : 1000         | 1 : 100          | /                |
| Chlorhexidine  | 4%            | Neat            | 1 : 10,000       | 1 : 1000         | /                |
| Povidone-iodine| 7.5%          | Neat            | 1 : 10,000       | 1 : 1000         | /                |

NMBAs, neuromuscular blocking agents.

Table 2: Concentrations of antibiotics used in skin testing.

| Agent            | Brand                      | SPT (mg/ml) | Initial step | Next step | IDT (mg/ml) |
|------------------|----------------------------|-------------|--------------|-----------|-------------|
| PPL              | Diater Laboratory, Spain   | 0.04        | 0.004        | 0.04      |             |
| MDM              | Diater Laboratory, Spain   | 0.5         | 0.05         | 0.5       |             |
| BP               | Genus Pharmaceuticals      | 6           | 6            | /         |             |
| Amoxicillin      | Bowmed                     | 25          | 2.5          | 25        |             |
| Flucloxacillin   | Wockhardt                  | 25          | 12.5         | 25        |             |
| Clavulanic acid  | Diater Laboratory, Spain   | 20          | 5            | 20        |             |
| Cefuroxime       | Fresenius Kabi             | 3.75        | 0.375        | 3.75      |             |

In cases with a history of severe reactions, the concentration might start with a lower dilution. SPT, skin prick test; IDT, intradermal test; PPL, penicilloyl poly-L-lysine; MDM, minor determinant mixture; BP, benzylpenicillin.

Latex

All patients were tested with SPT, when SPT was equivocal, sIgE for latex were performed
using commercial standardised products. If latex allergy was strongly suspected and skin test and sIgE were negative, a subsequent ‘prick-prick’ test with a latex glove was also performed. If the ‘prick-prick’ test was negative, then glove challenge (exposing the patient to latex by wearing a latex glove) was performed. If the glove challenge was negative, buccal challenge was performed.

Antiseptics
All patients were tested with antiseptic used during the surgery. Chlorhexidine skin test results were confirmed with sIgE.

Opiates and NSAIDs
Non-IgE-mediated systemic reaction/anaphylaxis was diagnosed for drugs, including opiates and non-steroidal anti-inflammatory drugs (NSAIDs), when there was a clear temporal association with the respective drug, and allergy tests were negative for other drugs and agents that were potentially implicated. However, challenge was considered if there was uncertainty in the clinical history.

Results
In total, 31 patients were referred during the designated period and completed the investigation. The patients included 19 females and 12 males, and the mean age was 48 ± 18 (standard deviation) years, with a range of 18 to 83. The median time from the index reaction to allergy testing was 3 (2–8, interquartile range) months. Most patients (23, 77.4%) were non-atopic in background.

The culprit drug was identified in 21 patients (67.7%). No cause could be identified in six patients (19.4%), despite full investigations. Clinical history suggested non-anaphylactic reactions in four patients (12.9%), but full investigations were performed to eliminate the possibility of allergic causation.

In the 21 patients in whom the culprit drug was detected, the following drugs were involved: antibiotics (n = 11, 52.3%), NMBAs (n = 8, 38.1%), morphine (n = 1, 4.8%) and gelofusine (n = 1, 4.8%). Among the eight patients who had reactions to NMBAs, nine positive skin tests were observed: four patients exhibited positive reactions to rocuronium, three patients exhibited reactions to atracurium, and one patient was found to exhibit reactions to both atracurium and suxamethonium (both of which were administered during anaesthesia). Furthermore, six patients had at least one positive result of cross-sensitisation to other NMBAs (Table 3).

Among the 10 patients who had reaction to antibiotics, three were allergic to penicillin and could tolerate cefuroxime challenge, two were allergic to clavulanic acid and one was allergic to flucloxacillin, (these three patients all tolerated amoxicillin challenge), three patients were allergic to teicoplanin, one was allergic to metronidazole, and one was allergic to rifampicin.

Among the 21 patients for whom the culprit drug was determined, tryptase measurements were available for 12 patients. Of those, nine patients had elevated levels. The remaining three patients had normal levels but suffered grade 3 reaction. Among the six patients for whom no cause was identified, four patients’ tryptase were available (three elevated and one normal) (Table 3).

Discussion
Allergological assessment of every patient who suffers anaphylaxis under GA is essential,11 and allergy centres that provide drug allergy evaluations play a crucial role in the prevention of future perioperative anaphylaxis.

In our series, the culprit drug was determined in 67.7% of patients, whereas the cause could not be identified in 19.4% of patients, even after repeated diagnostic workups for some individuals. A total of 12.9% were considered to have suffered non-allergic events. This finding illustrates the difficulty of allergy diagnosis in anaphylaxis during GA. The proportion of patients in our study for whom no causative agent could be determined was comparable to those in other reports.12–14

Among the 21 patients who suffered anaphylaxis during anaesthesia and the cause was subsequently identified, antibiotics were the most common causative agent (52.3%), followed by...
| Patient | Gender | Age | Time interval between reaction and assessment (months) | Severity | Tryptase test (ng/ml) | Culprit drug | Cross-reaction test | Remark |
|---------|--------|-----|-------------------------------------------------------|----------|----------------------|--------------|---------------------|--------|
| 1       | Male   | 30  | 1                                                    | 3        | 42.2 (first)         | Atra (1 : 1000 ID) | No cross-reaction    |        |
|         |        |     |                                                      |          | 5.1 (baseline)       |              |                     |        |
| 2       | Female | 51  | 1                                                    | 3        | NA                   | Roc (1 : 2 SPT)  | Vecu, Miva, Sux     |        |
| 3       | Male   | 48  | 8                                                    | 2        | NA                   | Atra (1 : 100 ID) | No cross-reaction    |        |
| 4       | Male   | 29  | 3                                                    | 3        | NA                   | Roc (1 : 200 ID)  | Vecu, Atra          |        |
| 5       | Female | 32  | 2                                                    | 3        | 36.5 (first)         | Sux (5 mg/ml SPT) | Vecu, Miva          |        |
|         |        |     |                                                      |          | 3.7 (baseline)       | Atra (1 : 1000 ID) |                     |        |
| 6       | Female | 30  | 2                                                    | 3        | NA                   | Roc (neat SPT)   | Vecu, Atra, Miva    | Tongue swelling, throat constriction during SPT |
| 7       | Male   | 36  | 3                                                    | 3        | 9.4 (first)          | Atra (SPT)      | Vecu                |        |
| 8       | Female | 54  | 1                                                    | 3        | 5.4 (first)          | Roc (1 : 200 ID) | Vecu, Atra, Sux     |        |
| 9       | Female | 57  | 1                                                    | 3        | 135 (first)          | PCN (PPL, AM, ID) | /                   | Tolerated Cef   |
|         |        |     |                                                      |          | 14.4 (baseline)      |              |                     |        |
| 10      | Male   | 28  | 6                                                    | 3        | 30.8 (first)         | PCN (PPL, AM, BP ID) | /                   | Tolerated Cef   |
|         |        |     |                                                      |          | 5.2 (baseline)       |              |                     |        |
| 11      | Male   | 83  | 3                                                    | 3        | 37.5 (first)         | PCN (sIgE to pen-V) | /                   | Tolerated Cef   |
|         |        |     |                                                      |          | 11.5 (baseline)      |              |                     |        |
| 12      | Female | 46  | 38                                                   | 3        | NA                   | CA (20 mg/ml ID) | /                   | Delayed skin reaction, tolerated AM |
| 13      | Female | 46  | 2                                                    | 3        | 31 (first)           | CA (20 mg/ml ID) | /                   | Tolerated AM    |
|         |        |     |                                                      |          | 4.2 (baseline)       |              |                     |        |
| 14      | Female | 54  | 4                                                    | 4        | 88.7 (first)         | Metro (1 : 1000 ID) | /                   |        |
|         |        |     |                                                      |          | 14.8 (baseline)      |              |                     |        |
| 15      | Male   | 77  | 4                                                    | 3        | 80 (first)           | Rif (0.006 mg/ml ID) | /                   |        |
|         |        |     |                                                      |          | 21.6 (baseline)      |              |                     |        |
| 16      | Male   | 67  | 8                                                    | 3        | NA                   | Teico (4 mg/ml ID) | /                   | Negative skin test, diagnosed from temporal association and negative tests to other drugs |
| 17      | Female | 54  | 1                                                    | 3        | 30.4 (first)         | Teico (0.4 mg/ml ID) | /                   | Anaphylaxis during testing |
|         |        |     |                                                      |          | 4.1 (baseline)       |              |                     |        |
| 18      | Male   | 38  | 4                                                    | 3        | 13.8 (first)         | Teico (0.4 mg/ml ID) | /                   |        |
|         |        |     |                                                      |          | 2.9 (baseline)       |              |                     |        |
| 19      | Female | 50  | 15                                                   | 3        | NA                   | Gelfusine (1 : 100 ID) | /                   |        |
| 20      | Female | 57  | 6                                                    | 1        | NA                   | Flu (12.5 mg/ml ID) | /                   | Tolerated Cef   |
| 21      | Female | 31  | 16                                                   | 1        | NA                   | Morphine (challenge subcutaneous) | /                   | No cross-reaction with codeine |
| 22      | Male   | 46  | 2                                                    | 2        | 17 (first)           | /              | /                   | No cause detected Non-IgE-mediated reaction |
|         |        |     |                                                      |          | 9.5 (baseline)       |              |                     |        |
| 23      | Female | 76  | 1                                                    | 3        | 17.6 (first)         | /              | /                   | No cause detected Non-IgE-mediated reaction |
|         |        |     |                                                      |          | 4.4 (baseline)       |              |                     |        |
| 24      | Male   | 66  | 2                                                    | 3        | /                    | /              | /                   |        |
NMBAs (38.1%), opioids (4.8%) and gelofusine (4.8%). In contrast, data from 4000 patients reported by Mertes et al. indicated that NMBAs accounted for 63% of reactions, followed by latex (14%), hypnotics (7%), antibiotics (6%), plasma substitutes (3%) and opioids (2%). In our study, antibiotics were the most common cause of anaphylaxis, whereas none of the adverse reactions were attributable to latex or hypnotics. These differences might be due to the small size of our study, which was limited to one centre and thus may not be representative.

Within the N MBA family, rocuronium was the most common culprit drug, followed by atracurium and suxamethonium. Although, no conclusions can be drawn as to the incidence of anaphylaxis with rocuronium from our small sample, previous studies published in France, Norway and Australia indicated a higher rate of anaphylaxis with rocuronium than other NMBAs. A 7-year, retrospective, observation cohort study conducted in New Zealand demonstrated that, although the rate of anaphylaxis is extremely rare, it appears to be approximately 10-fold higher to rocuronium than to atracurium.

The clinical histories indicated that only two of our patients had prior surgery and thus may have been sensitised to NMBAs via prior exposure. Fisher et al. also reported that in the case

### Table 3 (Continued)

| Patient | Gender | Age (months) | Severity (months) | Tryptase test (ng/ml) | Culprit drug | Cross-reaction test | Remark |
|---------|--------|--------------|--------------------|-----------------------|--------------|---------------------|--------|
| 50 (first) | 8.5 (baseline) | | | No cause detected | Non-IgE-mediated reaction |
| 25 Female | 18 | 2 | 2 | 3.7 (first) | / | / | No cause detected |
| 26 Female | 34 | 3 | 3 | NA | / | / | Possible non-IgE-mediated reaction |
| 27 Male | 35 | 37 | 2 | NA | / | / | Possible non-IgE-mediated reaction |
| 28 Male | 54 | 4 | / | NA | / | / | Non-anaphylaxis reaction (bronchospasm) (heavy smoker) |
| 29 Female | 53 | 13 | / | NA | / | / | Non-anaphylaxis reaction (bronchospasm) (had asthma) |
| 30 Female | 47 | 9 | / | NA | / | / | Non-anaphylaxis reaction (airway bleeding) |
| 31 Female | 21 | 6 | / | 1.8 (first) | 1.6 (baseline) | / | Non-anaphylaxis reaction (brief period of hypotension that was easily reversed) |

Atra, atracurium; Roc, rocuronium; Vecu, vecuronium; Miva, mivacurium; Sux, suxamethonium; NA, not available; PCN, penicillin; PPL, penicilloyl poly-L-lysine; MDM, minor determinant mixture; BP, benzylpenicillin; AM, amoxicillin; Flu, flucloxacillin; Pen-V, penicillin V; CA, clavulanic acid; Cef, cefuroxime; Metro, metronidazole; Teico, teicoplanin; Rif, rifampcin; SPT, skin prick test; ID, intradermal test.
of NMBA-induced allergy, only approximately 15% of affected subjects have ever been exposed to NBMAs previously. Why do NMBAs deviate from accepted mechanisms underlying IgE-mediated allergic reactions? The explanation might be that the origin of allergic sensitisation is an environmental agent or another drug containing an ammonium ion which has been confirmed to be the main allergenic structure of NMBAs. Recently, Florvaag et al. suggested that sensitisation with pholcodine could increase the titre of specific IgEs to quaternary ammonium ions and thereby increase the risk of allergic reaction to NMBAs.

The extent of allergenic cross-sensitisation between NMBAs has been estimated to be approximately 65% by skin testing and 80% by IgE tests. A total of 75.0% of our patients allergic to NMBAs had cross-sensitisation with other NMBAs upon further testing, consistent with published data. Six patients showed cross-sensitisation with vecuronium (2 at 1 : 100 and 4 at 1 : 10 concentration). It has been recommended that vecuronium should be tested at a lower concentration of 1 : 100 and hence we may have overestimated vecuronium cross-sensitisation.

In our study, two patients were allergic to clavulanic acid, both tolerated amoxicillin on subsequent challenge. Although initially considered as nonimmunogenic, recent studies indicate that immediate selective reactions to clavulanic acid account for approximately 22–30% of immediate allergic reactions to co-amoxiclav.

Three of our patients were diagnosed with teicoplanin allergy. Teicoplanin is a glycopeptide antibiotic that is now a first-line prophylactic therapy for orthopaedic, cardiac, breast, gastrointestinal, vascular and plastic procedures and is frequently used as a second-line therapy in penicillin-allergic patients. Anaphylaxis to teicoplanin was previously considered extremely rare, but in recent years, with the increase in prescribing, allergic reactions appear to be more common than previously thought. Patient No 16 developed anaphylaxis 30 min after uneventful induction and immediately after IV teicoplanin and gentamicin infusion. In view of negative challenge to gentamicin and negative skin tests to teicoplanin were negative, a likely diagnosis of teicoplanin allergy was made. Attempts to challenge the patient were not performed due to his comorbidities. Savic et al. suggested that the paradox of negative teicoplanin skin testing despite dramatic clinical presentations indicates that mast cell and possibly basophil activation might be caused by direct cell stimulation not involving IgE, or the concentration of the dilution used for testing might be sub-optimal. Of the remaining two patients who were diagnosed with teicoplanin allergy, one (No 17) suffered anaphylaxis during intradermal testing and the other skin tested positive (Table 3). The mechanism underlying teicoplanin allergy is not clear and further work is needed to establish an appropriate testing regimen for potential teicoplanin allergy.

We observed no sensitisation to latex, despite systematic testing of all of our patients. This finding was in accordance with recent data from four centres in the United Kingdom that implicated only one latex allergy (0.6%). This appears to be a general trend, as although previous French series indicated that latex was the second (17%) most frequent cause of perioperative anaphylaxis, more recent French series showed that latex is now only the fourth cause and the decrease in latex related anaphylaxis is likely due to primary and secondary prevention measures.

Serum tryptase is an indicator of mast cell degranulation and tends to be elevated in both IgE-mediated and non-IgE-mediated anaphylaxis. Guidelines suggest serial measurements of serum tryptase including baseline value. However, practical experience suggests that this recommendation is not always followed. In our study, only 54.8% of the referred patients underwent tryptase testing. There is no consensus regarding the threshold level of tryptase for the diagnosis of anaphylaxis. In this study, the normal range was set at 2–14 μg/l. Serum tryptase > 25 μg/l is highly suggestive of an IgE-mediated mechanism. Recently, Laroche et al. proposed the optimal threshold 7.35 μg/l, resulting in 92% sensitivity and 92% specificity. Using the upper level of normal values, 12.5 μg/l and 25 μg/l, sensitivity was calculated as 82.7% and 68%, respectively, and specificity was 96% and 100%,
respectively. Krishna proposed that an acute serum tryptase level elevated from baseline (percentage change > 141%, absolute quantification change > 15.7 μg/l) is highly predictive of IgE-mediated anaphylaxis, whereas Sprung et al. recommended that the clinically significant elevation be at least 2 + 1.2 × baseline level. In our study, most of the patients in the culprit drug detected-group who underwent tryptase measurement exhibited elevated levels > 25 μg/l, with the exception of three patients (No7, 8 and 18) who had normal levels but suffered from grade 3 reactions (patient 18 tested positive by Sprung criteria). Normal tryptase levels do not exclude the possibility of anaphylaxis, which can remain normal in 36% of patients who had clinically defined anaphylaxis. A possible explanation is anaphylaxis attributed to local release of tryptase (e.g. in laryngeal oedema), which may not be sufficient to increase the total serum tryptase concentration; alternatively, there may be a greater participation of basophils than mast cells in the mechanism of anaphylaxis in some situations. Although there are limitations in the use of this biomarker, interpreting the result in the context of the clinical picture, and the baseline level of tryptase, provides useful information.

In the no-cause-identified group, three patients had elevated tryptase both by our and Sprung criteria and one had normal tryptase. According to Gurrieri et al., they could be classified as non-IgE and possible non-IgE mediated anaphylaxis, but it is also possible that our investigations or the clinical history missed hidden IgE-mediated culprit. Tryptase was not available for two patients and hence we were not able to comment on the mechanism of their reaction.

In conclusion, this study has demonstrated that in the United Kingdom, antibiotics and NMBAs are commonly implicated as causative agents of perioperative anaphylaxis. Despite the constant expansion of knowledge, the diagnosis of anaphylaxis during GA remains challenging for both anaesthetists and allergists.

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Reference

1. Mertes PM, Laxenaire MC. GERAP [Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France. Seventh epidemiologic survey (January 2001-December 2002)]. Ann Fr Anesth Reanim 2004; 23: 1133–43.
2. Mertes PM, Laxenaire MC, Alla F. Groupe d’Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003; 99: 536–45.
3. Laxenaire MC. [Epidemiology of anesthetic anaphylactoid reactions Fourth multicenter survey (July 1994-December 1996)]. Ann Fr Anesth Reanim 1999; 18: 796–809.
4. Fisher M, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. Eur J Anaesthesiol 1994; 11: 263–84.
5. Mertes PM, Malinovský JM, Jouffroy L. Working Group of the SFAR and SFA, Aberer W, Terreehorst I, Brockow K, Demoly P; ENDA; EAACI Interest Group on Drug Allergy. Reducing the risk of anaphylaxis during anaesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol 2011; 21: 442–53.
6. Gibbs NM, Sadleir PH, Clarke RC, Platt PR. Survival from perioperative anaphylaxis in Western Australia 2000–2009. Br J Anaesth 2013; 111: 589–93.
7. Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugue P, Friedmann PS, English JS, Huber PA, Nasser SM, BSACI. BSACI guidelines for the management of drug allergy. Clin Exp Allergy 2009;39:43–61.
8. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002; 57: 45–51.
9. Romano A, Bousquet-Rouanet L, Viola M, Gaeta F, Demoly P, Bousquet PJ. Benzylpenicillin skin testing is still important in diagnosing immediate hypersensitivity reactions to penicillins. Allergy 2009; 64: 249–53.
10. Mirakian R, Leech SC, Krishna MT, Richter AG, Huber PA, Farooque S, Khan N, Pirmohamed M, Clark AT, Nasser SM. Management of allergy to penicillins and other beta-lactams. Clin Exp Allergy 2015; 45: 300–27.
11. National Clinical Guideline Centre. Drug Allergy: diagnosis and Management of Drug Allergy in Adults, Children and Young People. London: National Institute for Health and Care Excellence (UK), 2014.
12. Krishna MT, York M, Chin T, Gnanakumaran G, 
   Heslegrave J, Derbridge C, Huissoon A, Diwakar L, 
   Eren E, Crossman RJ, Khan N, Williams AP. Multi-
   centre retrospective analysis of anaphylaxis during 
   general anaesthesia in the United Kingdom: 
   aetiology and diagnostic performance of acute 
   serum tryptase. Clin Exp Immunol 2014; 178: 399– 
   404.

13. Antunes J, Kochuyt AM, Ceuppens JL. 
   Perioperative allergic reactions: experience in a 
   Flemish referral centre. Allergol Immunopathol 
   2014; 42: 348–54.

14. Gurrieri C, Weingarten TN, Martin DP, Babovic N, 
   Narr BJ, Sprung J, Volcheck GW. Allergic reactions 
   during anesthesia at a large United States referral 
   center. Anest Analg 2011; 113: 1202–12.

15. Florvaag E, Johansson S-G, Öman H, Venemalm L, 
   Degerbeck F, Dybendal T, Lundberg M. Prevalence 
   of IgE antibodies to morphine. Relation to the high 
   and low incidences of NMBA anaphylaxis in 
   Norway and Sweden, respectively. Acta 
   Anaesthesiol Scand 2005; 49: 437–44.

16. Sadleir P, Clarke R, Bunning D, Platt P. 
   Anaphylaxis to neuromuscular blocking drugs: 
   incidence and cross-reactivity in Western Australia 
   from 2002 to 2011. Br J Anaesth 2013; 110: 981–7.

17. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam 
   JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more 
   common with rocuronium and succinylcholine than 
   with atracurium. J Am Soc Anesthesiology 2015; 
   122: 39–45.

18. Fisher MM, Munro I. Life-threatening 
   anaphylactoid reactions to muscle relaxants. Anest 
   Analg 1983; 62: 559–64.

19. Baldo BA, Fisher MM, Pham NH. On the origin 
   and specificity of antibodies to neuromuscular 
   blocking (muscle relaxant) drugs: an 
   immunochemical perspective. Clin Exp 
   Immunol 2009; 39: 325–44.

20. Florvaag E, Johansson SG. The pholcodine story. 
   Immunol Allergy Clin North Am 2009; 29: 419–27.

21. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, 
   Stevens WJ. Anaphylaxis during anaesthesia: 
   diagnostic approach. Allergy 2007; 62: 471–87.

22. Ewan PW, Dugue P, Mirakian R, Dixon TA, Harper 
   JN, Nasser SM, BSACI. BSACI guidelines for the 
   investigation of suspected anaphylaxis during 
   general anaesthesia. Clin Exp Allergy 2010;40:15–31.

23. Brockow K, Garvey LH, Aberer W, Atanaskovic-
   Markovic M, Barbaud A, Bilo MB, Bircher A, 
   Blanca M, Bonadonna B, Campi P, Castro E, 
   Cernadas JR, Chiriac AM, Demoly P, Grosber M, 
   Gooi J, Lombardo C, Mertes PM, Mosbech H, 
   Nasser S, Pagani M, Ring J, Romano A, Scherer K, 
   Schnyder B, Testi S, Torres M, Trautmann A, 
   Terreehorst I. Group EEDAI. Skin test 
   concentrations for systemically administered drugs 
   – an ENDA/EAACI Drug Allergy Interest Group 
   position paper. Allergy 2013; 68: 702–12.

24. Edwards RG, Dewney JM, Dobrzanski RJ, Lee D. 
   Immunogenicity and allergenicity studies on two 
   beta-lactam structures, a clavam, clavulanic acid, 
   and a carbapenem: structure-activity relationships. 
   Int Arch Allergy Appl Immunol 1988; 85: 184–9.

25. Torres MJ, Ariza A, Mayorga C, Dona I, Blanca-
   Lopez N, Rondon C, Blanca M. Clavulanic acid can 
   be the component in amoxicillin-clavulanic acid 
   responsible for immediate hypersensitivity 
   reactions. J Allergy Clin Immunol 2010; 125: 502-
   05 e2.

26. Blanca-Lopez N, Perez-Alzate D, Ruano F, 
   Garcimartin M, de la Torre V, Mayorga C, Somoza 
   ML, Perkins J, Blanca M, Canto MG, Torres MJ. 
   Selective immediate responders to amoxicillin and 
   clavulanic acid tolerate penicillin derivative 
   administration after confirming the diagnosis. 
   Allergy 2015; 70: 1013–9.

27. Savic S, Teicoplanin allergy - an emerging problem in 
   the anaesthetic allergy clinic. Br J Anaesth 2015; 
   115: 595–600.

28. Mertes PM, Volcheck GW, Garvey LH, Takazawa T, 
   Platt PR, Guttmersen AB, Tacquard C. 
   Epidemiology of perioperative anaphylaxis. Presses 
   Medicale 2016; 45: 758–67.

29. Laroche D, Gomis P, Gallimidi E, Malinovsky JM, 
   Barbaud A, Bilo MB, Bircher A, 
   Blanca M, Bonadonna B, Campi P, Castro E, 
   Cernadas JR, Chiriac AM, Demoly P, Grosber M, 
   Gooi J, Lombardo C, Mertes PM, Mosbech H, 
   Nasser S, Pagani M, Ring J, Romano A, Scherer K, 
   Schnyder B, Testi S, Torres M, Trautmann A, 
   Terreehorst I. Group EEDAI. Skin test 
   concentrations for systemically administered drugs 
   – an ENDA/EAACI Drug Allergy Interest Group 
   position paper. Allergy 2013; 68: 702–12.

30. Sprung J, Weingarten TN, Schwartz LB. Presence or 
   absence of elevated acute total serum tryptase by 
   itself is not a definitive marker for an allergic 
   reaction. Anesthesiology 2015; 122: 713–4.

31. Sala-Cunill A, Cardona V, Labrador-Horrillo M, 
   Luengo O, Esteso O, Garriga T, Vicario M, Guilarte 
   M. Usefulness and limitations of sequential serum 
   tryptase for the diagnosis of anaphylaxis in 102 
   patients. Int Arch Allergy Immunol 2013; 160: 192– 
   9.

32. Michalska-Krzanowska G. Tryptase in diagnosing 
   adverse suspected anaphylactic reaction. Adv Clin 
   Exp Med 2012; 21: 403–8.