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

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Background: Anaphylaxis during general anaesthesia is rare but often severe. Identification of the cause of anaphylaxis and recommendation of a range of drugs or agents likely to be safer for future surgery is a collaborative venture between the allergists and the anaesthesiologists, but it often poses a significant challenge.
Methods: A total of 31 patients who attended the Drug Allergy Unit at University College London Hospital with suspected perioperative anaphylaxis between March 2013 and January 2016 were reviewed retrospectively.
Results: The culprit drug was identified in 21 patients (67.7%): antibiotics (n = 11, 52.3%), neuromuscular blocking agents (n = 8, 38.1%), morphine (n = 1, 4.8%) and gelofusine (n = 1, 4.8%). No cause was identified in six patients (19.4%), and four patients (12.9%) had non-allergic reactions.
Conclusion: Our results confirm that antibiotics and neuromuscular blocking agents are common causative agents of perioperative anaphylaxis in the United Kingdom.

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 13,000,[1–3] 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

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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 (NMBA), 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

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 : 5000	1 : 500	/
Rocuronium	10 mg/ml	1 : 2	1 : 20,000	1 : 2000	1 : 200	/
Vecuronium	4 mg/ml	1 : 10	1 : 10,000	1 : 1000	1 : 100	1 : 10
Mivacurium	2 mg/ml	1 : 2	1 : 10,000	1 : 1000	/	/
Atracurium	10 mg/ml	1 : 10	1 : 10,000	1 : 1000	/	/
Pancuronium	2 mg/ml	1 : 10	1 : 10,000	1 : 1000	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 : 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
Alfentanyl	0.5 mg/ml	Neat	/	1 : 1000	1 : 100	1 : 10
Remifentanyl	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.

(BP) and amoxicillin. 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 2 Concentrations of antibiotics used in skin testing.

Agent	Brand	SPT (mg/ml)	IDT (mg/ml)	
			Initial step	Next step
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 identified 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

Table 3 Clinical details of patients' demographics and drug allergy testing results.

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) 5.1 (baseline)	Atra (1 : 1000 ID)	No cross-reaction	
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) 3.7 (baseline)	Sux (5 mg/ml SPT) Atra (1 : 1000 ID)	Vecu, Miva	
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) 5.6 (baseline)	Atra (SPT)	Vecu	
8	Female	54	1	3	5.4 (first) 4.5 (baseline)	Roc (1 : 200 ID)	Vecu, Atra, Sux	
9	Female	57	1	3	135 (first) 14.4 (baseline)	PCN (PPL, AM, ID)	/	Tolerated Cef
10	Male	28	6	3	30.8 (first) 5.2 (baseline)	PCN (PPL, AM, BP ID)	/	Tolerated Cef
11	Male	83	3	3	37.5 (first) 11.5 (baseline)	PCN (sIgE to pen-V)	/	Tolerated Cef
12	Female	46	38	3	NA	CA (20 mg/ml ID)	/	Delayed skin reaction, tolerated AM
13	Female	46	2	3	31 (first) 4.2 (baseline)	CA (20 mg/ml ID)	/	Tolerated AM
14	Female	54	4	4	88.7 (first) 14.8 (baseline)	Metro (1 : 1000 ID)	/	
15	Male	77	4	3	80 (first) 21.6 (baseline)	Rif (0.006 mg/ml ID)	/	
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) 4.1 (baseline)	Teico (0.4 mg/ml ID)	/	Anaphylaxis during testing
18	Male	38	4	3	13.8 (first) 2.9 (baseline)	Teico (0.4 mg/ml ID)	/	
19	Female	50	15	3	NA	Gelofusine (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) 9.5 (baseline)	/	/	No cause detected Non-IgE-mediated reaction
23	Female	76	1	3	17.6 (first) 4.4 (baseline)	/	/	No cause detected Non-IgE-mediated reaction
24	Male	66	2	3		/	/	

Table 3 (Continued)

Patient	Gender	Age	Time interval between reaction and assessment (months)	Severity	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) 2.9 (baseline)	/	/	No cause detected Possible non-IgE-mediated reaction
26	Female	34	3	3	NA	/	/	No cause detected Possible non-IgE-mediated reaction
27	Male	35	37	2	NA	/	/	No cause detected 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.

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%).[5] 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 NMBA 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,[2] Norway[15] and Australia[16] 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 to either rocuronium or atracurium is extremely rare, it appears to be approximately 10-fold higher to rocuronium than to atracurium.[17]

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

of NMBA-induced allergy, only approximately 15% of affected subjects have ever been exposed to NBMAs previously.[18] 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.[19] 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.[20]

The extent of allergenic cross-sensitisation between NMBAs has been estimated to be approximately 65% by skin testing and 80% by IgE tests.[21] A total of 75.0% of our patients allergic to NMBAs had cross-sensitisation with other NMBAs upon further testing, consistent with published data.[22] Six patients showed cross-sensitisation with vecuronium (2 at 1 : 100 and 4 at 1 : 10 concentration). It has been recommened that vecuronium should be tested at a lower concentration of 1 : 100 and hence we may have overestimated vecuronium cross-sensitisation.[23]

In our study, two patients were allergic to clavulanic acid, both tolerated amoxicillin on subsequent challenge. Although initially considered as nonimmunogenic,[24] recent studies indicate that immediate selective reactions to clavulanic acid account for approximately 22–30% of immediate allergic reactions to co-amoxiclav.[25,26]

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 testing to other possible culprits, although 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.[27]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%).[12] 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,[2] 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.[28]

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[1,24]. 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.[5] 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.[29] 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,[12] whereas Sprung et al. recommended that the clinically significant elevation be at least 2 + 1.2 × baseline level.[30] 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[30]). Normal tryptase levels do not exclude the possibility of anaphylaxis, which can remain normal in 36% of patients who had clinically defined anaphylaxis.[31]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.[32] 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[30] and one had normal tryptase. According to Gurrieri et al.,[14] 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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