

Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6)

N. J. N. Harper^{1,2,3}, T. M. Cook^{4,5,6,*}, T. Garcez⁷, L. Farmer³, K. Floss⁸, S. Marinho⁹, H. Torevell, A. Warner¹⁰, K. Ferguson¹¹, J. Hitchman³, W. Egner^{12,13}, H. Kemp¹⁴, M. Thomas¹⁵, D. N. Lucas¹⁶, S. Nasser¹⁷, S. Karanam¹⁸, K.-L. Kong¹⁸, S. Farooque¹⁹, M. Bellamy^{20,21} and N. McGuire²²

¹Manchester University NHS Foundation Trust, Manchester, UK, ²Manchester Academic Health Science Centre, University of Manchester, Manchester, UK, ³Royal College of Anaesthetists, London, UK, ⁴Royal United Hospital, Bath, UK, ⁵University of Bristol School of Medicine, Bristol, UK, ⁶Health Services Research Centre, Royal College of Anaesthetists, London, UK, ⁷Manchester University NHS Foundation Trust, Manchester, UK (United Kingdom Fatal Anaphylaxis Register), ⁸Oxford University Hospitals NHS Trust, Oxford, UK (Royal Pharmaceutical Society of Great Britain), ⁹Manchester University NHS Foundation Trust, Manchester, UK (British Society for Allergy and Clinical Immunology), ¹⁰Allergy UK, London, UK, ¹¹Aberdeen Royal Infirmary, Aberdeen, UK (Association of Anaesthetists of Great Britain and Ireland), ¹²Sheffield Teaching Hospitals NHS Trust, Sheffield, UK (Royal College of Physicians/Royal College of Pathologists Joint Committee on Immunology and Allergy), ¹³Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK, ¹⁴Imperial College London, UK (Research and Audit Federation of Trainees), ¹⁵Great Ormond Street Hospital, London, UK (Association of Paediatric Anaesthetists of Great Britain and Ireland), ¹⁶Northwick Park Hospital, Harrow, UK (Obstetric Anaesthetists' Association), ¹⁷Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK (British Society for Allergy and Clinical Allergy), ¹⁸Sandwell and West Birmingham NHS Trust, Birmingham, UK, ¹⁹Imperial College Healthcare NHS Trust, London, UK, ²⁰Leeds Teaching Hospitals NHS Trust, Leeds, UK (Faculty of Intensive Care Medicine), ²¹Leeds University, Leeds, UK and ²²Medicines and Healthcare products Regulatory Agency, London, UK

*Corresponding author. E-mail: timcook007@gmail.com

Editorial decision: April 13, 2018; Accepted: April 13, 2018

© 2018 British Journal of Anaesthesia. Published by Elsevier Ltd. All rights reserved.
For Permissions, please email: permissions@elsevier.com

Abstract

Background: Anaphylaxis during anaesthesia is a serious complication for patients and anaesthetists.

Methods: The 6th National Audit Project (NAP6) on perioperative anaphylaxis collected and reviewed 266 reports of Grades 3–5 anaphylaxis over 1 yr from all NHS hospitals in the UK.

Results: The estimated incidence was $\approx 1:10\,000$ anaesthetics. Case exclusion because of reporting delays or incomplete data means true incidence might be $\approx 70\%$ higher. The distribution of 199 identified culprit agents included antibiotics (94), neuromuscular blocking agents (65), chlorhexidine (18), and Patent Blue dye (9). Teicoplanin comprised 12% of antibiotic exposures, but caused 38% of antibiotic-induced anaphylaxis. Eighteen patients reacted to an antibiotic test dose. Succinylcholine-induced anaphylaxis, mainly presenting with bronchospasm, was two-fold more likely than other neuromuscular blocking agents. Atracurium-induced anaphylaxis mainly presented with hypotension. Non-depolarising neuromuscular blocking agents had similar incidences to each other. There were no reports of local anaesthetic or latex-induced anaphylaxis. The commonest presenting features were hypotension (46%), bronchospasm (18%), tachycardia (9.8%), oxygen desaturation (4.7%), bradycardia (3%), and reduced/absent capnography trace (2.3%). All patients were hypotensive during the episode. Onset was rapid for neuromuscular blocking agents and antibiotics, but delayed with chlorhexidine and Patent Blue dye. There were 10 deaths and 40 cardiac arrests. Pulseless electrical activity was the usual type of cardiac arrest, often with bradycardia. Poor outcomes were associated with increased ASA, obesity, beta blocker, and angiotensin-converting enzyme inhibitor medication. Seventy per cent of cases were reported to the hospital incident reporting system, and only 24% to Medicines and Healthcare products Regulatory Agency via the Yellow Card Scheme.

Conclusions: The overall incidence of perioperative anaphylaxis was estimated to be 1 in 10 000 anaesthetics.

Keywords: allergy; anaesthesia; anaphylaxis; National Audit Project

Anaphylaxis is defined as a severe, life-threatening generalised or systemic hypersensitivity reaction.¹ Most anaphylactic reactions are allergic. Severity is commonly graded 1–5, although multiple grading systems exist. Mild reactions, Grades 1 and 2, do not constitute anaphylaxis. The 6th National Audit Project (NAP6) investigated Grades 3–5 reactions occurring in the perioperative period. Estimates of the incidence of perioperative anaphylaxis vary between 1:6000 to 1:20 000 anaesthetics.² In a large French study, the estimated incidence of immunoglobulin E (IgE)-mediated perioperative hypersensitivity (Grades 1–4) was 1:10 000 anaesthetics.³ A UK questionnaire study of 4595 general anaesthetics estimated the incidence at 1:2297.⁴

Perioperative anaphylaxis can vary over time and between different patient populations. Most studies have identified neuromuscular blocking agents (NMBAs) as the commonest culprit agents. In a French study, latex was the second commonest cause of anaphylaxis, unlike in a more recent UK study.⁵ The majority of previous reports have included all grades of perioperative hypersensitivity, and all report similar patterns of clinical features. In a small number of cases, there can be single organ-system involvement,³⁵ and cutaneous features predominate in mild, non-IgE-mediated perioperative hypersensitivity.³⁵ The clinical features of severe anaphylaxis are very similar regardless of whether allergic or non-allergic. It is important to understand how severe anaphylaxis presents, as there is a wide differential diagnosis; no bedside testing; and a prompt, specific treatment is essential.^{6–8}

There are few large prospective studies of perioperative anaphylaxis with most looking retrospectively at cases that have been referred to allergy clinics for investigation. In addition, few studies have focused solely on severe (Grades 3–5) perioperative anaphylaxis or investigated relationships between presenting features and co-morbidities or

concomitant medication. Individual trigger agents can elicit disparate patterns of presentation, including onset time, cardiovascular or respiratory system preponderance and outcomes can also differ: for example, the onset of anaphylaxis to chlorhexidine, latex, and Patent Blue dye can be delayed.^{7,9–11}

Methods

Methods are discussed in detail in an accompanying paper, but are described here briefly for clarity.¹² Denominator data included all cases under the care of an anaesthetist and were derived from the NAP6 Activity Survey¹³ and NAP6 Allergen Survey.¹⁴ Cases were reported using a two-part form: Part A reported soon after the anaphylactic event and Part B after the allergy clinic letter had been received by the anaesthetist. We defined allergic anaphylaxis by the presence of onset within 60 min, evidence of mast-cell mediator release (mast-cell tryptase), evidence of positive specific IgE (blood or skin tests), and exclusion of differential diagnoses. Four positive criteria were necessary for 'high' certainty and three for 'intermediate' certainty, but evidence of positive specific IgE (blood or skin tests) was essential for both levels of certainty. Non-allergic anaphylaxis was defined by the absence of positive specific IgE (blood or skin tests), but required onset within 60 min, evidence of mast-cell mediator release (mast-cell tryptase), and exclusion of differential diagnoses; four criteria for 'high' certainty; and three criteria for 'intermediate' certainty. Further information on the criteria for mast-cell tryptase positivity is given in the accompanying Methods paper.¹² Trigger agents were identified based on clinical history and allergy clinic investigations. The degree of certainty of attribution was achieved using rules described in the Methods paper, and was categorised as 'definite', 'probable', 'possible', or 'do not count'; only the first two categories were considered confirmed triggers.¹²

Results

Of 541 cases reported, 412 included both Part A and Part B, or were fatalities (10). One hundred and forty-six cases were excluded as a result of lack of detail or not meeting the criteria (93), being uninterpretable (27), being judged not anaphylaxis (15), or Grade 2 (9), and two were from non-NHS hospitals.¹² We identified 266 cases of Grades 3–5 anaphylaxis meeting our inclusion criteria. The Activity Survey¹³ estimated that 3 126 067 anaesthetics were delivered in the UK in 2016, giving a calculated incidence of perioperative anaphylaxis of 1:11 752 [95% confidence interval (CI): 10 422–13 303].

Of 199 culprit agents (in 192 cases), 148 were identified as 'definite' and 51 as 'probable' (including seven cases where two probable culprits were identified). In 15 cases, the culprit was designated 'possible', and in 57 cases, the culprit could not be identified. The most common causes of perioperative anaphylaxis were antibiotics, followed by neuromuscular blocking agents, chlorhexidine, and Patent Blue dye (Table 1). Most (58%) anaphylactic events occurred in the operating theatre, and 3% were before the induction of anaesthesia, 81% after the induction and before surgery, 13% during surgery, and 3% after surgery.

The incidences of the four most prevalent groups of drugs or agents were:

- (i) Antibiotics: 92/2 469 754 = 1 in 26 845 (95% CI: 1 in 21 889–1 in 33 301)

Table 1 The 199 identified culprit agents in 192 cases of anaphylaxis in NAP6.

	Definite	Probable	Total
Agents by class			
Antibiotics	67	27	94
Neuromuscular blocking agents	49	16	65
Chlorhexidine	14	4	18
Patent Blue dye	8	1	9
Other agents	10	3	13
All	148	51	199
Antibiotics			
Co-amoxiclav	38	8	46
Teicoplanin	21	15	36
Cefuroxime	2	2	4
Gentamicin	1	2	3
Flucloxacillin	2	0	2
Piperacillin and tazobactam	1	0	1
Vancomycin	1	0	1
Metronidazole	1	0	1
Neuromuscular blocking agents			
Rocuronium	21	6	27
Atracurium	14	9	23
Succinylcholine	13	1	14
Mivacurium	1	0	1
Antiseptics and dyes			
Chlorhexidine	14	4	18
Patent Blue dye	8	1	9
Other agents			
Gelatin	3	0	3
Blood products	2	0	2
Ondansetron	1	1	2
Sugammadex	1	0	1
Ibuprofen	1	0	1
Propofol	1	0	1
Protamine	1	0	1
Aprotinin	0	1	1
Heparin	0	1	1

- (ii) Neuromuscular blocking agents: 64/1 220 465 = 1 in 19 070 (95% CI: 1 in 14 934–1 in 24 762)
- (iii) Chlorhexidine: 18/2 298 567 = 1 in 127 698 (95% CI: 1 in 80 800–1 in >150 000)
- (iv) Patent Blue dye: 9/61 768 = 1 in 6863 (95% CI: 1 in 3616–1 in 15 009)

Clinical features

The first clinical features were hypotension (46%), bronchospasm/high airway pressure (18%), tachycardia (9.8%), cyanosis/oxygen desaturation (4.7%), bradycardia (3%), and reduced or absent capnography trace (2.3%) (Fig. 1). Three patients presented with cardiac arrest (1.2%). Bronchospasm was the presenting feature more frequently in morbidly obese compared with other patients (Fig. 2) and in (mainly well-controlled) asthmatic patients (34%) compared with non-asthmatic patients (15%).

Presentation was similar regardless of whether the mechanism was allergic or non-allergic. In approximately 1 in 20 cases, an awake patient reporting feeling unwell was the harbinger of anaphylaxis (Fig. 1). Fifteen (5.6%) patients presented with isolated cardiovascular features and four (1.5%) with isolated respiratory features.

Hypotension as the presenting feature was proportionately more common in men than in women, perhaps related to coronary artery disease (24% vs 8.4%), beta blockers (27% vs 11%), and angiotensin-converting enzyme (ACE) inhibitor medication (21.2% vs 15.2%). Bronchospasm was more common in women: more women had asthma (25% vs 16%) (Supplementary Fig. S1). There was a marked difference between NMBAs: bronchospasm was the most common presentation when succinylcholine (suxamethonium) was the trigger and hypotension with atracurium (Fig. 3).

Considering the clinical features present at any time during the anaphylactic episode, hypotension was universal. Rash, seldom a presenting feature, developed in 56% of cases; bronchospasm/high airway pressure in 48%; tachycardia in 46%; cyanosis/oxygen desaturation in 41%; and a reduced/absent capnography trace in 33%. Bronchospasm at any time was also seen in a higher proportion of patients with asthma (59%) than others (46%). Again, this clinical pattern was very similar in the subgroup of allergic anaphylaxis patients (Fig. 4).

Two notable features were almost absent. Rash was an uncommon presenting feature and was notably rare at any time in the most serious of cases. Airway problems were also rarely seen. A single patient required a front-of-neck airway to manage laryngeal oedema, but there were no other presentations or significant clinical features of airway difficulty.

Considering all cases, the onset time was <5 min in 66%, <10 min in 83%, <15 min in 88%, and <30 min in 95%. The onset times for individual agents are discussed below.

Fatalities, cardiac arrests, and profound hypotension

Ten patients died directly (eight) or indirectly (two) as a result of anaphylaxis, equating to an incidence of perioperative death from anaphylaxis of 1 in 313 000 and a per-case mortality rate of 1 in 26.6 cases. All fatalities were aged >46 yr, and half aged >66 yr. Two were ASA 2, six were ASA 3, and two were ASA 4. In the Activity Survey,¹³ 25% of patients were aged >66 yr, 77% were ASA 1–2, and <2% were ASA 4–5.

Only one patient was of normal weight; four were overweight, one was obese, and four were morbidly obese. In the Activity Survey,¹³ 21% of all patients were obese or morbidly obese. None of the patients who died had a history of atopy or

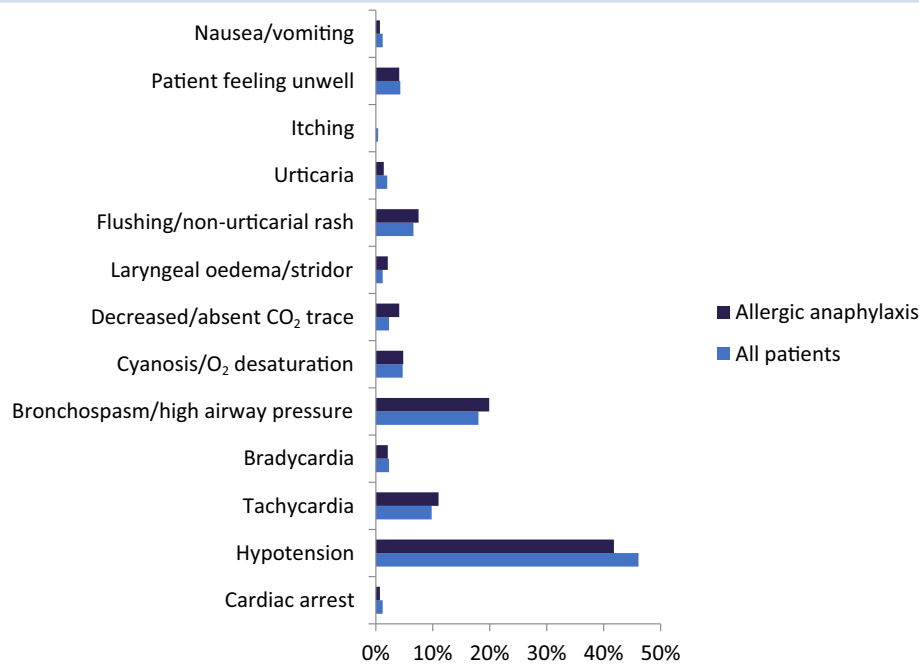


Fig 1. First clinical feature (%) in allergic anaphylaxis and all patients with Grades 3–5 perioperative anaphylaxis.

asthma. Five had coronary artery disease, most of whom were undergoing non-cardiac surgery; six were taking beta blockers and six were taking ACE inhibitors. Three were taking both and one patient was taking neither drug. Amongst the 266 reports of life-threatening anaphylaxis, 15% had evidence of coronary artery disease, 17% were taking beta blockers, and 17% were taking ACE inhibitors. Three of 10 patients were undergoing cardiac surgery. The surgical procedure was abandoned in nine cases and proceeded in one.

Cardiac arrest occurred during the event in nine of 10 patients who died, and was pulseless electrical activity (PEA) in all fatal cases; none preceded by significant arrhythmias, although there was bradycardia in two. Management of these cases is described in the accompanying paper.¹⁵

Forty (15%) patients, all of whom were adults, experienced cardiac arrest and 31 (78%) survived (Table 2). Most (81%) events occurred after the induction of anaesthesia and before surgery. A consultant was involved in all resuscitations. No particular trigger agents were associated with a higher risk of cardiac arrest. However, the survivors of cardiac arrest were younger, fitter, and had fewer co-morbid conditions than patients who died (Table 3).

The presenting features are shown in Fig. 5. Hypotension and bronchospasm/raised airway pressure were prominent, and rash was notably uncommon. Reduced or absent capnogram trace was not recorded as a presenting feature in any cases. Bradycardia was more common than tachycardia. Cardiovascular presenting features occurred in 25, respiratory in

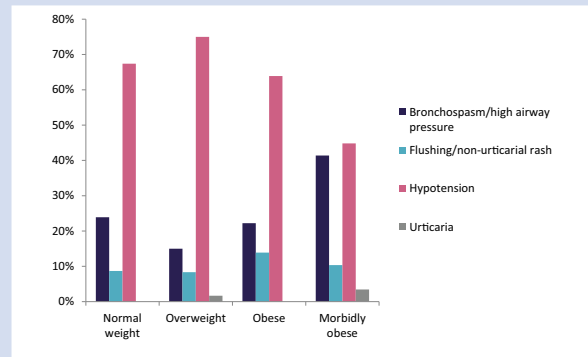


Fig 2. Presenting feature and body habitus in Grades 3–5 perioperative anaphylaxis.

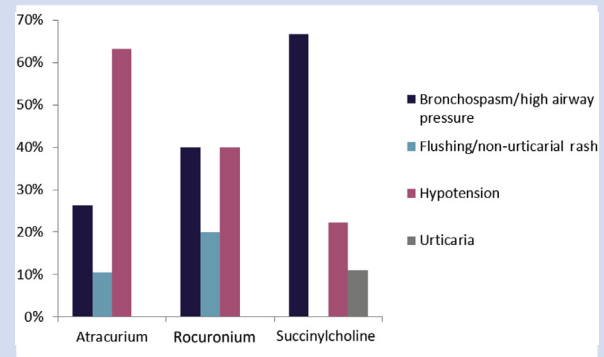


Fig 3. Initial features of Grades 3–5 neuromuscular blocking agent-induced anaphylaxis.

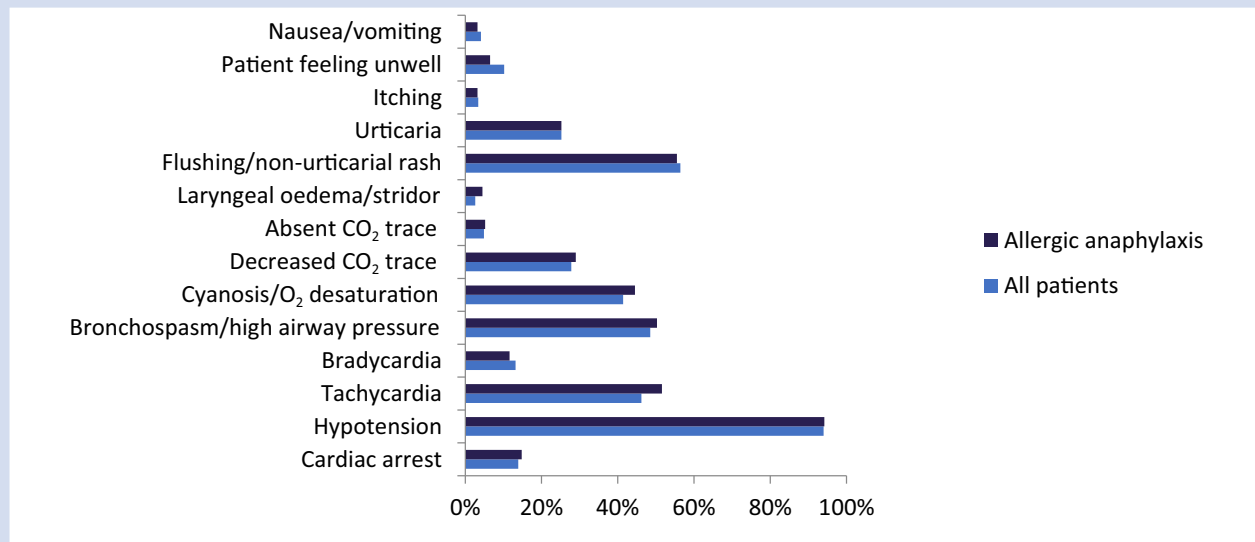


Fig 4. Clinical features (%) present at any time during Grades 3–5 perioperative anaphylaxis: allergic anaphylaxis and all patients.

Table 2 Comparison of patients who survived or died after perioperative anaphylaxis

	Died after anaphylaxis, n=10 (%)	Survived anaphylaxis, n=256 (%)
Age >66 yr	40	31
Obese or morbidly obese	50	36
Coronary artery disease	50	13
Taking beta blocker	60	15
Taking angiotensin-converting enzyme inhibitor	60	21
Asthma	0	21

11, and others in four. Of all cardiac arrests, 34 were PEA, four ventricular fibrillation/pulseless ventricular tachycardia, and two were asystole. Only six patients developed an arrhythmia before cardiac arrest: four bradycardia and two ventricular tachycardia. There were no reports of atrial fibrillation or supraventricular tachycardia. In adult patients, the lowest

systolic BP recorded in the first hour after the event was 'unrecordable' in 56 (21%) cases, <50 mm Hg in 58 (22%) cases, and 51–59 mm Hg in 53 (20%) cases.

Antibiotics

Ninety-two cases of antibiotic-induced anaphylaxis were identified (including 94 definite or probable antibiotic culprits); 48% of all cases with identified culprits. The majority were caused by co-amoxiclav or teicoplanin, between them accounting for 89% of identified antibiotic culprits. The overall incidence of reported antibiotic-induced anaphylaxis was 4.0 per 100 000 exposures. The highest incidence was seen with teicoplanin (16.4 per 100 000 exposures) then co-amoxiclav (8.7 per 100 000 exposures). The relative anaphylaxis rate using cefuroxime as an index was 17.4 for teicoplanin and 9.2 for co-amoxiclav (Table 4). Of the 10 deaths, four were judged to be caused by an antibiotic.

The incidences of the three most prevalent antibiotics were:

- (i) Co-amoxiclav: 46/532 580 = 1 in 11 578 (95% CI: 1 in 8680–1 in 15 814)

Table 3 Characteristics of patients who died compared with those who survived cardiac arrest, or experienced or did not experience profound hypotension

	Deaths, n=10 (%)	Non-fatal cardiac arrest, n=31 (%)	BP <50 mm Hg without cardiac arrest or death, n=79 (%)	All others, n=135 (%)
Age >66 yr	50	35	33	34
ASA physical status ≥ 3	80	13	33	27
Obesity	50	31	34	43
Coronary artery disease	50	8	15	14
Beta blocker	60	7	14	19
Angiotensin-converting enzyme inhibitor	60	32	9	17
Asthma	0	14	19	24

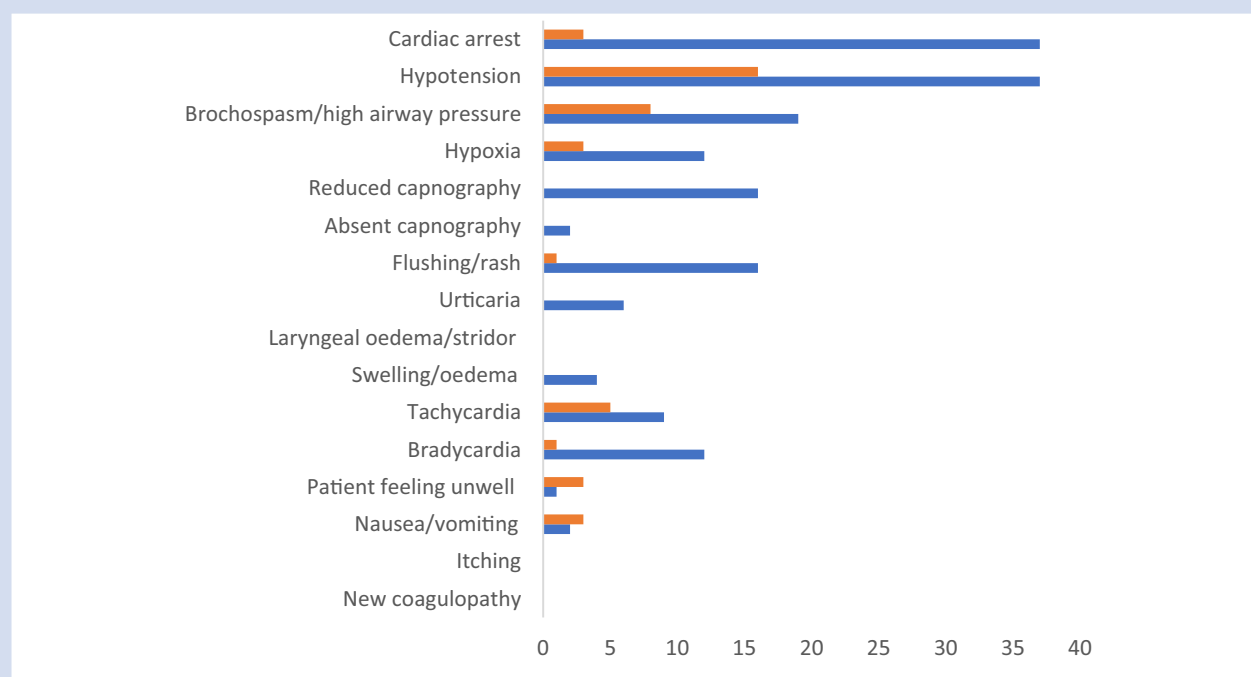


Fig 5. Clinical features of 37 non-fatal cardiac arrests from perioperative anaphylaxis (presenting, and at any time): orange, presenting feature; blue, during event.

- (ii) Teicoplanin: 36/219 621 = 1 in 6101 (95% CI: 1 in 4407–1 in 8710)
- (iii) Cefuroxime: 4/424 143 = 1 in 106 035 (95% CI: 1 in 41 414–1 in >150 000).

The onset of anaphylaxis was within 5 min in 74% of cases, 18% between 6 and 10 min, 5% between 11 and 15 min, and 2% between 16 and 30 min. None were delayed >30 min.

Of the 36 patients who reacted to teicoplanin, 20 (56%) stated before operation that they were allergic to penicillin. Of the 36 reactions, 16 were Grade 3, 18 were Grade 4, and 2 were Grade 5. Ten developed moderate and two severe harm (death). Amongst the 20 who likely received teicoplanin because of a history of allergy, two reactions were Grade 4 and one was Grade 5; six developed moderate harm and one died.

The NAP6 Allergen Survey¹⁴ demonstrated the choice of antibiotic was influenced by preoperative allergy history in a quarter of patients who received teicoplanin or vancomycin. In <1% of cases, communication failure led to an antibiotic being administered despite a relevant positive allergy history. Two cases were judged preventable by better allergy history communication.

There were 18 antibiotic-related reactions related to test doses: in 10 (53%) cases, the patient reacted to the test dose itself, which ranged from 5% to 30% of the therapeutic dose, and the other eight patients reacted to the full dose, which was given within 1 min of the test dose in all but one case (given within 10 min). There was no evidence that administration of a 'test dose' of antibiotic reduced the severity of an ensuing

Table 4 Estimated incidences for antibiotic-induced anaphylaxis with definite or probable attribution in NAP6. *Annual usage identified from the Allergen Survey¹⁴

	Culprits identified by the review panel	Proportion of antibiotic usage (%)*	Patients receiving the drug per annum*	Anaphylaxis rate per 100 000 administrations	Relative rates (cefuroxime=1)
Co-amoxiclav	46	29.8	532 580	8.7	9.2
Teicoplanin	36	12.3	219 621	16.4	17.4
Cefuroxime	4	23.7	424 143	0.94	1.0
Gentamicin	3	34.5	616 899	0.49	0.5
Flucloxacillin	2	11.9	211 973	0.94	1.0
Piperacillin and tazobactam	1	1.6	28 237	3.5	3.7
Vancomycin	1	1.0	17 648	5.7	6.1
Metronidazole	1	15.2	272 173	0.37	0.4
Total (all antibiotic administrations)	94 culprits (92 cases)	100	2 323 274	4.0	4.2

reaction. In contrast, in cases of anaphylaxis caused by an antibiotic where a test dose had been given, a slightly greater proportion of severe reactions (Grades 4 and 5) was seen than if no test dose had been given (58% vs 51%).

Neuromuscular blocking agents and reversal agents

Triggers were identified as neuromuscular blocking agents in 64 cases, 25% of all cases, including 32% of cases leading to cardiac arrest or death. Ninety-five per cent of NMBA-induced reactions presented within 5 min. The culprit neuromuscular blocking agents were rocuronium (42% of cases), atracurium (35%), succinylcholine (22%), and mivacurium (1.5%). There were no cases of anaphylaxis caused by vecuronium, pancuronium, or cisatracurium, although these only accounted for 4.4% of all neuromuscular blocking agent use.¹⁴ The review panel identified non-allergic anaphylaxis to atracurium in three cases, and to mivacurium in a single case. The incidence per 100 000 exposures is a more meaningful metric than the occurrence rate. The overall incidence of reported neuromuscular blocking agent-induced anaphylaxis was 5.3 per 100 000 exposures. The highest incidence was seen with succinylcholine (11.1 per 100 000 exposures), while all others were similar to each other. Succinylcholine was twice as likely to cause anaphylaxis than any other neuromuscular blocking agent (Table 5).

The incidences of the three most prevalent neuromuscular blocking agents was:

- (i) Rocuronium: 27/459 047 = 1 in 17 002 (95% CI: 1 in 11 686–1 in 25 799)
- (ii) Atracurium: 23/554 543 = 1 in 24 111 (95% CI: 1 in 16 069–1 in 38 034)
- (iii) Succinylcholine: 14/126 086 = 1 in 9006 (95% CI: 1 in 5368–1 in 16 473).

In 71% of cases where the anaesthetist suspected an neuromuscular blocking agent, the culprit was confirmed by the panel, and in 14%, an alternative culprit was identified. The ratio of suspected/confirmed cases was 1.4 for atracurium, 1.3 for rocuronium, and 1.1 for succinylcholine (Table 5).

Previous exposure to pholcodine was recorded in only two patients, both of whom had neuromuscular blocking agent-induced anaphylaxis (rocuronium and succinylcholine), but no conclusions can be drawn because of a very limited recording of pholcodine exposure. No episodes were caused by neostigmine. The anaesthetist suspected that sugammadex was the suspected trigger agent in two cases, and one of these

was confirmed by the review panel. The Allergen Survey¹⁴ estimated 64 121 annual exposures to sugammadex.

Chlorhexidine

There were 18 cases of chlorhexidine-induced anaphylaxis, representing 9% of culprits. The Allergen Survey¹⁴ identified 2 298 567 exposures to chlorhexidine by at least one route annually (74% of all cases). Based on NAP6 data, the incidence of anaphylaxis to chlorhexidine is 0.78 per 100 000 exposures, likely an overestimate, as almost all patients are exposed to chlorhexidine during anaesthesia and surgery.

Despite reporting chlorhexidine allergy before the event, one patient was exposed, resulting in anaphylaxis. One patient reported a prior reaction during anaesthesia that was not investigated and reacted to chlorhexidine when exposed. One patient experienced a subsequent reaction to chlorhexidine despite confirmation of allergy to chlorhexidine after an investigation of the index NAP6 event. There was one fatal reaction. Eight reactions were Grade 4 and nine were Grade 3. Consistent with published data, most cases were in males (16/18). Ten patients were ASA 2 and eight were ASA 3. Urology (six cases), cardiac (three cases), and orthopaedic (three cases) surgery accounted for the majority of cases.

The anaesthetist suspected chlorhexidine in only five (28%) cases. Reactions to cutaneous chlorhexidine were mostly slower than other agents and of lower grade. There was quicker onset and greater severity in patients with exposure via a coated central venous catheter (CVC) (mostly onset <5 min of exposure and Grade 4 events) than those with only topical surgical site exposure (mostly onset at 1 h and Grade 3 events). Approximately two-thirds of cases presented with hypotension and none presented with bronchospasm (Supplementary Fig. S2).

Patent Blue dye

We identified nine (3.4%) cases of Patent Blue dye-induced anaphylaxis: five were Grade 3 and four were Grade 4. Based on an estimated 61 768 annual exposures,¹⁴ the incidence of anaphylaxis to Patent Blue dye was 14.6 per 100 000 administrations (i.e. higher than succinylcholine). All patients were female: eight were scheduled for breast cancer surgery, and this was abandoned in two cases.

Onset was slower than other trigger agents with only two cases <5 min, four presented after >15 min, including two after >60 min. Hypotension was the commonest presentation: all patients became significantly hypotensive, and in three cases,

Table 5 Neuromuscular blocking agents confirmed as causative agents by the panel: absolute and relative risk. NMBA, neuromuscular blocking agent. *Data from the NAP6 Allergen Survey.¹⁴

	Cases suspected by anaesthetist	Cases confirmed by review panel	Proportion of UK NMBA usage (%) [*]	Patients receiving the drug per annum [*]	Anaphylaxis rate per 100 000 administrations	Relative risk of anaphylaxis (atracurium=1)
Rocuronium	34	27	40.6	459 047	5.88	1.42
Atracurium	32	23	49.1	554 543	4.15	1
Succinylcholine	16	14	11.2	126 086	11.1	2.67
Mivacurium	0	1	2.7	30 786	3.25	0.78
Vecuronium	0	0	2.2	24 315	—	—
Cisatracurium	0	0	1.6	18 629	—	—
Pancuronium	0	0	0.6	7059	—	—

systolic BP fell below 50 mm Hg. Four patients desaturated to <90%. Cutaneous features were present in six patients. All cases were resuscitated successfully, and no long-term physical sequelae were reported.

Miscellaneous trigger agents

We identified three cases of anaphylaxis to succinylated gelatin solutions and two to blood products. Ondansetron, propofol, aprotinin, protamine, and ibuprofen were responsible for a very small number of cases. The Allergen Survey estimated that 48 203 UK patients are exposed to gelatin-based i.v. fluids during anaesthesia each year,¹⁴ giving an approximate incidence of 6.2 per 100 000 administrations, a rate similar to rocuronium.

Reporting

As reporting is a positive action, it was inferred that this did not take place where the information was not provided. Nine per cent of cases were reported to Medicines and Healthcare products Regulatory Agency (MHRA) by the anaesthetist, 8.3% by the Local Coordinator, 3% by the allergy clinic, and 2.6% by others, including critical care staff. Only three deaths and nine of 31 who survived cardiac arrest (29% combined) were reported to the MHRA.

Reporting to the Trust's critical reporting incident system was performed in 70% of cases (including eight of 10 deaths, and 24 (77%) of 31 cardiac-arrest survivors). Of these 187 cases, 160 were reported by an anaesthetist, six by the nursing team, and five by the surgical team.

Discussion

The overall incidence of perioperative anaphylaxis was estimated to be 1 in 10 000 anaesthetics. This may be an underestimate. We excluded 17.5% of cases with a Parts A and B form. If all 541 submissions had included both parts of the form and the same proportion (17.5%) were excluded, the maximum number of cases of anaphylaxis would have been 446, an increase of 67%. This equates to an incidence of 1:7000 cases. As we do not know why, for many cases, some parts of the forms were not submitted, we cannot state whether this higher estimate is reliable.

Previous estimates of incidence of hypersensitivity are similar, but the majority included perioperative hypersensitivity of all grades: despite including only Grades 3–5, our estimated incidence is at least as high. It is possible that the incidence of perioperative anaphylaxis is rising, perhaps as a result of increasing antibiotic sensitisation in the population, and it is notable that antibiotics have overtaken neuromuscular blocking agents as the most frequent trigger agents. Irrespective of absolute incidences, because of our methodology, we believe our results accurately represent the relative incidence with different trigger agents.

Presenting features

Perioperative anaphylaxis has several unusual if not unique elements. First, the vast majority of triggers are administered intravenously, therefore, having the potential for the most rapid and severe reactions. Second, multiple drugs are administered almost concurrently. These routinely alter normal physiology, such that hypotension, arrhythmia, bronchospasm, and even rash may be more commonly

attributable to causes other than anaphylaxis. Lastly, the events occur in the immediate presence of a trained 'resuscitator' who may be able to identify and manage the event more promptly than in many other settings.

Variations in presenting clinical features between different patient groups, with different drugs and with different severities of reactions, are all notable and add to the available literature. It is worth noting that hypotension was universal. Bronchospasm was less common, but was more often seen in the obese and those with pre-existing asthma. Rash was rarely present, sometimes missed (the patient hidden under drapes) and was particularly uncommon in the most severe cases, often only occurring when BP and presumably perfusion had been restored. Bradycardia was relatively common, again in the more severe events, and arrhythmias were rare. Airway complications were almost absent.

Fatalities

Our data suggest that perioperative anaphylaxis was more likely to be fatal in patients who were older, of a higher ASA physical status, and significantly obese. Unlike anaphylaxis in the community,¹⁶ we found no evidence of asthma as a risk factor for fatal perioperative anaphylaxis, but coronary artery disease and administration of beta blockers and/or ACE inhibitors were prominent. Patients died despite prolonged attempts at resuscitation, with most aspects of care being rated as good as described in detail in the accompanying paper.¹⁵

Cardiac arrest and survivors

Most patients who survived cardiac arrest were younger and fitter than those who died. Prescription of ACE inhibitors was again prominent in those who developed cardiac arrest. A considerable majority of cardiac arrests were PEA, and the absence of tachyarrhythmias either as a primary event or secondary to epinephrine (adrenaline) administration is notable.

Profound hypotension

A group of patients, who had profound hypotension, without being designated as 'in cardiac arrest', was identified during review as an apparently high-risk cohort with some poor outcomes. There was discussion regarding the point at which cardiac compressions should be started and, after seeking wide expert advice, we agreed this should be 50 mm Hg, so any patient with a lowest systolic BP <50 mm Hg was designated as requiring cardiopulmonary resuscitation, and therefore, Grade 4, and where cardiac compressions were not started, this was judged to have been an omission. This is a newly identified group and perhaps contentious. Their management and outcomes are discussed in the accompanying paper.¹⁵

Antibiotics

In contrast to many published series,^{3,17,18} antibiotics, not neuromuscular blocking agents, were the most common causes of perioperative anaphylaxis. The high frequency of teicoplanin-induced anaphylaxis is noteworthy and likely presents an upward trend. Our findings demonstrate that the administration of teicoplanin is closely related to patient-reported penicillin allergy, the most commonly reported drug allergy in the community with up to 10% of the

population labelled as allergic. It is likely that the majority are mislabelled and that at least 90% could be de-labelled if an adequate description of the original reaction could be obtained or the patient was investigated in an allergy clinic.¹⁹

More than half of all cases received an antibiotic, almost all of which were administered after the induction of anaesthesia, with signs of anaphylaxis identified in <5 min in most cases and almost all in <10 min. Anaphylaxis-induced hypotension is likely to be exacerbated by general or neuraxial anaesthesia. Therefore, there is a strong argument for antibiotics to be administered several minutes before the induction of anaesthesia. There are several potential benefits: first, lack of known allergy can be confirmed with the patient immediately before administration; second, the severity of physiological derangement caused by anaphylaxis might be less; and third, investigation of anaphylaxis is considerably simplified if fewer drugs have been administered.

It is likely that some of the anaphylactic reactions to antibiotics could have been avoided. This is particularly likely to be the case in patients reported to be allergic to penicillin who were then given teicoplanin, which had a 17-fold higher risk of anaphylaxis than flucloxacillin (or cefuroxime). If it were possible to identify the >90% of patients who report penicillin allergy, but who are not, then avoidance of second-line antibiotics would likely lessen the overall risk of perioperative anaphylaxis significantly. Of note, second-line antibiotics are more expensive and, particularly when used for treatment, are associated with increased duration of treatment, hospital stay, and antibiotic resistance.^{20–22} It is currently impractical for all putative penicillin allergy to be investigated in allergy clinics before operation, and the process is significantly complex. However, with the ever-increasing importance of antibiotic stewardship, avoidance of a spurious label of 'penicillin allergic' is an area ripe for research.

Thirteen patients with anaphylaxis caused by co-amoxiclav and four of those with anaphylaxis to teicoplanin had received an i.v. 'test dose' of between 5% and 30% of the therapeutic dose. It cannot reasonably be expected that a single test dose will eliminate the risk of anaphylaxis. In the allergy clinic, the starting dose for drug challenge (which starts only after negative skin testing) will vary depending on the severity of the index reaction, the dose that is believed to have caused it, the patient's concurrent co-morbidities, whether the challenge is oral or i.v., and the drug itself. With some high-risk drug challenges, this can be as low as 0.1% of the therapeutic dose increasing in 2- to 10-fold increments. NAP6 provides evidence that anaphylaxis occurring after a test dose is no less severe than after a full dose. A third of UK anaesthetists routinely administer a test dose when administering an i.v. antibiotic,²³ despite guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) advising against their use,⁷ and we find no evidence to support the practice.

Neuromuscular blocking agents and reversal agents

In previous studies, neuromuscular blocking agents (NMBAs) were responsible for 40–66% of all cases of perioperative anaphylaxis.^{18,24} Sensitisation to NMBAs can occur during anaesthesia, but the majority of patients do not give a history of previous exposure,²⁵ and environmental exposure to the quaternary ammonium epitope has been implicated in generating NMBA allergy.²⁶ In addition, pholcodine-containing cough medicines might cause sensitisation to NMBAs²⁷: NMBA

sensitisation has declined in Norway since the withdrawal of pholcodine cough medicine.²⁸

Non-allergic anaphylaxis can occur with atracurium and mivacurium. Recent evidence implicates specific receptors on the surface of mast cells.²⁹ Variation in receptor expression might explain why these drugs cause dramatic non-IgE-mediated mediator release in some individuals.

No previous study has undertaken parallel investigation of incidence and NMBA exposure during a 1 yr period. In a study of concomitant exposure and anaphylaxis rates over a 6 yr period, the pattern of perioperative anaphylaxis might not have been constant.³⁰ Studies relying on sales of drug ampoules to estimate the number of patient exposures may not estimate the denominator accurately. Ampoule sales of succinylcholine likely overestimate usage as a result of waste. To avoid these pitfalls, NAP6 surveyed the number of patients receiving NMBAs during the same year as the case-reporting phase.

NMBAs accounted for about one-third fewer cases of anaphylaxis than antibiotics, but carry at least as high a risk as antibiotics per administration, with the exception of teicoplanin. The lower occurrence rate of NMBA-induced anaphylaxis observed is caused by ≈ 2.5 million administrations of antibiotics to surgical patients per year compared with ≈ 1.2 million administrations of NMBAs. Succinylcholine is well known to carry a greater risk of anaphylaxis than other NMBAs, which our data confirm. The risk of succinylcholine-induced anaphylaxis was about twice that of all other NMBAs.

It has been suggested previously that rocuronium is associated with a relatively higher risk of anaphylaxis than vecuronium.³¹ In that study, the incidence of succinylcholine anaphylaxis could not be accurately estimated through lack of denominator data. Vecuronium is used only rarely in the UK.¹⁴ Although our data cannot be definitive regarding the relative incidence of atracurium- and rocuronium-induced anaphylaxis, we identified no major difference in their observed incidences, and our data should not be interpreted as indicating that rocuronium is a more frequent culprit than atracurium. The difficulties inherent in interpreting the reported incidences of uncommon anaphylactic events have been described.³² In particular, marginal under-reporting has a disproportionately large effect on calculated incidence when the event being recorded occurs only very rarely. Anaesthetists tended to overestimate the number of cases caused by NMBAs, perhaps as a result of their well-known allergenic potential.

We are unable to comment on the possible influence of pholcodine consumption on the incidence of NMBA anaphylaxis. This information was not recorded in two-thirds of reports, and only 18% of allergy clinics routinely seek this information.³³

A single case of sugammadex-induced anaphylaxis was reported. Onset was delayed, and anaphylaxis should be considered among other differential diagnoses if a patient deteriorates in the recovery room. Sugammadex used as treatment for anaphylaxis is discussed in the accompanying paper.¹⁵

Chlorhexidine

Perioperative chlorhexidine exposure can occur via topical skin disinfection, chlorhexidine-coated CVCs, and use of chlorhexidine-containing lubricating gels.⁹ It might not be

immediately obvious that these products contain chlorhexidine, which has been called 'the hidden allergen'.³⁴

There are geographical differences in the incidence of chlorhexidine-induced perioperative anaphylaxis: 7.7% in the UK³⁵ and 9.3% in Denmark³⁶; rare in France.³⁷ The cause for the variation is not clear, but might be related to under-recognition and differences in practice (e.g. more use of povidone iodine and lower use of chlorhexidine-coated catheters). As exposure to chlorhexidine is highly likely in any surgical setting, several centres routinely test all patients referred with perioperative anaphylaxis for chlorhexidine allergy. In countries adopting this practice, chlorhexidine allergy is generally commonly identified.^{35,36}

Sensitisation to chlorhexidine can occur in healthcare settings or the community, as chlorhexidine-containing products are found in both environments.^{38,39} The true prevalence of chlorhexidine allergy remains unknown. During a 10 yr period up to 2004, only 50 cases of IgE-mediated reactions were reported in the medical literature. More recently, 104 cases were reported from four UK specialist centres covering only 2009–2013.¹⁰

Chlorhexidine is not yet considered among the 'mainstream' causes of perioperative anaphylaxis, despite evidence to the contrary. This is reflected by lost opportunities during perioperative history taking and the low suspicion rate we observed. Previously, up to 80% of patients diagnosed with chlorhexidine allergy reported possible chlorhexidine allergy that could have been identified before their adverse reaction.^{39,40}

Despite an alert relating to chlorhexidine-containing medical products and devices being issued nationally by MHRA in 2012,⁴¹ it appears that many clinical staff are unaware of which products contain this antiseptic and the risks of anaphylaxis. It is unsurprising that reactions are more rapid and severe when a CVC is the source of the chlorhexidine and the allergen is delivered directly to the circulation. Removing the CVC is central to treating the reaction under these circumstances.

Patent Blue dye

Patent Blue dye is found as a food dye (E131), approved for use in the UK, but not in the USA, Australasia, Japan, and several other countries. It structurally resembles other triaryl-methane dyes widely used in manufacturing. During surgery, it is injected into the tissues and taken up by the lymphatic system enabling sentinel lymph nodes to be seen directly. Sensitisation is likely caused by environmental exposure to the dye or a cross-reacting epitope. The reported estimated incidence of allergic reactions, which are commonly mild, varies between 150 and 1000 per 100 000 administrations.^{11,42–44} Reactions are frequently delayed 30–60 min, possibly because of the slow absorption from subcutaneous tissues and lymphatics.⁴³

As Patent Blue dye interferes with pulse oximetry (causing spuriously low readings), there is a potential delay in the recognition of onset of anaphylaxis. While two studies examining this effect reported mean reductions in digital oxygen saturation (SpO₂) of <2%,^{11,45} in some individuals, considerably greater falls can be observed.^{46,47}

In NAP6, reactions to Patent Blue dye were relatively common, were severe, and required significant resuscitation. Cutaneous signs were absent in a third of patients, and absence of rash should not dominate the differential

diagnosis. As hypoxaemia is common after perioperative anaphylaxis, any fall in oxygen saturation should be assumed to be real until a blood gas analysis has ruled this out.

Miscellaneous agents

The very small number of cases of reactions to blood products (and none to red blood cells) is notable. The Activity Survey estimated approximately 84 000 perioperative administrations of blood products. The relative infrequency of these is perhaps attributable to the success of the serious hazards of transfusion haemovigilance scheme (<https://www.shotuk.org/>).⁴⁸

Ondansetron is administered during an estimated 77% of general anaesthetics and 66% of all cases involving anaesthetist-delivered care.¹⁴ Just two cases report of ondansetron-induced anaphylaxis indicates its extreme rarity. However, these reactions can be severe: two cases of fatal anaphylaxis attributed to ondansetron have been reported.⁴⁹

We observed a single case of propofol allergy. Propofol is an extremely uncommon cause of anaphylaxis. Our survey data indicate that well over 2 million patients in the UK are exposed to this induction agent perioperatively each year.¹⁴ Twenty-four IgE-mediated cases were reported in a French 8 yr study³ and two cases were recorded in a UK 7 yr single-clinic study.⁵ Propofol-induced anaphylaxis might occur in some patients via a non-IgE-mediated mechanism.⁵⁰ Skin testing is negative in this situation, and controlled provocation testing with i.v. propofol would be necessary to confirm the diagnosis, a procedure that is not generally available. The same publication dispelled the notion that propofol is contra-indicated in adults who are allergic to egg, soya, or peanut, but some uncertainty still exists in children who have experienced anaphylaxis to egg.⁵¹ A diagnosis of hypersensitivity to propofol has serious implications for the patient, given the ubiquity of this induction agent, and therefore, merits a full investigation.

We recorded one case of anaphylaxis to protamine in a patient with diabetes mellitus. It has been suggested that patients who have been exposed to neutral protamine Hagedorn insulin, which contains protamine, are more likely to experience protamine-induced anaphylaxis.⁵² Fish allergy has been implicated as a risk factor for protamine anaphylaxis, as protamine is traditionally extracted from the sperm of fish. This risk may decrease as the drug becomes increasingly synthesised by recombinant biotechnology.

Anaphylaxis caused by non-steroidal anti-inflammatory drugs (NSAIDs) has been comprehensively reviewed.⁵³ There is a wide spectrum of severity and pathogenesis. Reactions are commonly non-immunologically mediated and there can be cross-reactivity to drugs sharing cyclooxygenase-1 enzyme inhibition. An 8 yr national study in France identified only three immunologically mediated perioperative hypersensitivity reactions to NSAIDs.³

Reporting

Reporting of cases of anaphylaxis to the hospital and the MHRA was disappointingly low. All NAP6 cases were at least Grade 3, representing a life-threatening incident, yet almost a third were not reported to the hospital's critical incident reporting system, reducing the likelihood of lessons being learned where applicable. Few cases were reported to the MHRA despite AAGBI guidance to do so, irrespective of severity

of the outcome. Local Coordinators were responsible for many of the reports to the MHRA, so in normal circumstances, such reporting might be even lower. Our data imply that pharmacovigilance is not being supported adequately, and further mean that data reported back to anaesthetists and allergy clinics by the MHRA are likely to be unreliable. Factors contributing to poor reporting-rates have been discussed.⁵⁴

Conclusions

We believe this is the largest study of life-threatening perioperative anaphylaxis that incorporates contemporaneous real-life data on exposure to potential allergens, permitting the calculation of accurate relative-incidence rates. Antibiotic allergy is an increasing problem, particularly to teicoplanin; optimising the preoperative allergy history could reduce the number of these perioperative anaphylactic reactions. Our data should dispel any notion that test doses prevent or ameliorate anaphylaxis. An awake patient is able to report early symptoms of evolving anaphylaxis, and our data support administering antibiotics before the induction of anaesthesia if practical. Early recognition is key to a successful treatment, and our results show that the initial presentation can be varied, likely to be bronchospasm if succinylcholine is the trigger agent, and can be delayed, particularly with Patent Blue dye and some exposures to chlorhexidine, the 'hidden allergen'. Patient factors, such as ASA physical status, obesity, and use of beta blockers and ACE inhibitors, influence the clinical features of perioperative anaphylaxis, a dimension previously under-reported. Risk of anaphylaxis should not be a determining factor in the choice between rocuronium and atracurium. Anaesthetists should report cases through the MHRA Yellow Card Scheme so that pharmacovigilance can be better supported in the future. This is the first of two companion papers describing the main findings of NAP6; in the second,¹⁵ we describe clinical management and outcomes, and make recommendations for organisational and individual practice.

Authors' contributions

Study design: N.J.N.H., T.M.C.

Study methodology: All authors.

Results analysis: All authors.

Writing of drafts, including final draft: N.J.N.H.

Review and revision of drafts: T.M.C.

Contributed to the design and methodology of the study, reviewed the results, and took part in the review of draft manuscripts leading to finalisation: all other panel members.

Acknowledgements

The authors thank all anaesthetists who engaged with the NAP6 project and all Local Coordinators who administered the project at each of the participating hospitals. At the Royal College of Anaesthetists, the authors thank J. Goodwin (Research Manager), J. Lourtie (Research Supervisor), and S. Drake (Director of Education and Research). The authors also acknowledge the contributions of the following NAP6 panel review members: S.R. Moonesinghe, University College Hospital London NHS Trust, London, UK (Health Services Research Centre); A. McGlennan, Royal Free London NHS Foundation Trust, London, UK; G. Scadding, Royal Brompton and Harefield NHS Foundation Trust, London, UK; T.

Krishna, Heart of England NHS Foundation Trust, Birmingham, UK; R. Collins, Hillsborough Private Clinic (The Association for Perioperative Practice); and M. East, Former National Coordinator of the Anaphylaxis Campaign (Anaphylaxis Campaign).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.bja.2018.04.014>.

Declaration of interest

T.M.C. is an associate editor of the *British Journal of Anaesthesia*. He is not aware of any financial conflicts. All other authors declare that they have no conflicts of interest.

Funding

The Royal College of Anaesthetists.

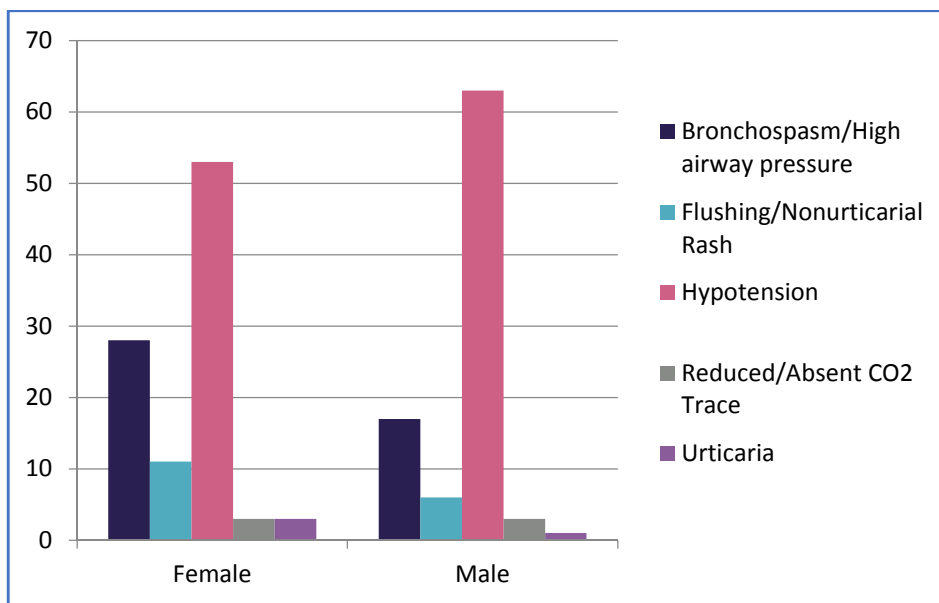
References

1. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EEACI position statement from the EEACI nomenclature task force. *Allergy* 2001; **56**: 813–24
2. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; **97**: 1381–95
3. Mertes PM, Alla F, Tréchet P, et al. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011; **128**: 366–73
4. Savic L, Kaura V, Yusaf M, et al. Incidence of suspected perioperative anaphylaxis: a multicentre snapshot study. *J Allergy Clin Immunol Pract* 2015; **3**: 454–455.e1
5. Low AE, McEwan JC, Karanam S, North J, Kong KL. Anaesthesia-associated hypersensitivity reactions: seven years' data from a British bi-specialty clinic. *Anaesthesia* 2016; **71**: 76–84
6. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian clinical practice guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
7. Harper NJN, Dixon T, Dugue P, et al. Guidelines suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
8. Kolawole H, Marshall S, Crilly H, Kerridge R, Roessler P. Australian and New Zealand Anaesthetic Allergy Group/ Australian and New Zealand College of Anaesthetists Perioperative Anaphylaxis Management Guidelines. *Anaesth Intensive Care* 2017; **45**: 151–8
9. Parkes AW, Harper N, Herwadkar A, Pumphrey R. Anaphylaxis to the chlorhexidine component of Instillagel: a case series. *Br J Anaesth* 2009; **102**: 65–8
10. Egner W, Helbert M, Sargur R, et al. Chlorhexidine allergy in four specialist allergy centres in the United Kingdom, 2009–13: clinical features and diagnostic tests. *Clin Exp Immunol* 2017; **188**: 380–6
11. Mertes PM, Malinovsky JM, Mouton-Faivre C, et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol* 2008; **122**: 348–52
12. Cook TM, Harper NJN, Farmer L, et al. Anaesthesia, surgery and life-threatening allergic reactions: protocol and

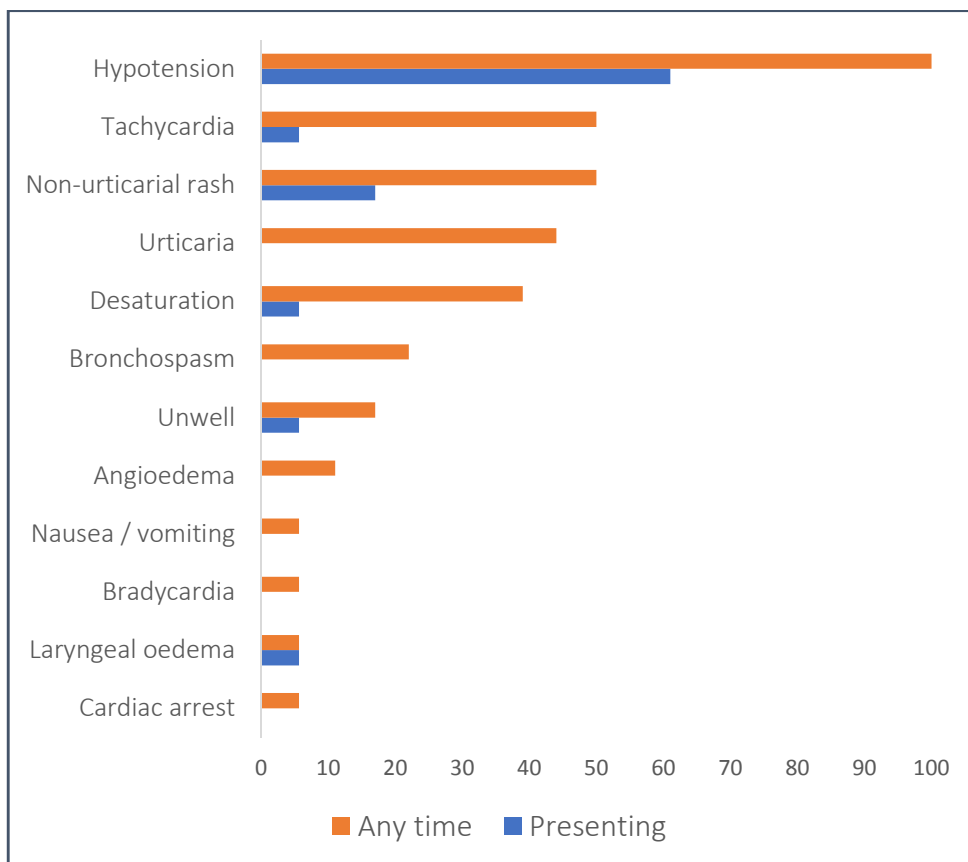
- methods of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists. *Br J Anaesth* 2018; **121**: 124–33
13. Kemp H, Marinho S, Cook TM, et al. A cross-sectional study of anaesthetic workload in the United Kingdom in 2016: the NAP6 Activity Survey. *Br J Anaesth* 2018. In press
 14. Marinho S, Kemp H, Cook TM, et al. A cross-sectional study of anaesthetic drug exposure in United Kingdom practice. The NAP6 Allergen Survey. *Br J Anaesth* 2018. In press
 15. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery and life-threatening allergic reactions: management, outcomes and recommendations in the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists. *Br J Anaesth* 2018; **121**: 172–88
 16. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; **30**: 1144–50
 17. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology* 2005; **102**: 897–903
 18. Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during general anaesthesia: a 10-year survey 1 at the University Hospital of Antwerp. *P Belg Royal Acad Med* 2013; **2**: 88–100
 19. National Institute for Health and Clinical Excellence. CG 183. *Drug allergy: diagnosis and management of drug allergy in adults, children and young people*. 2014. p. 1–167. <https://www.nice.org.uk/guidance/CG183>. [Accessed 3 May 2018]
 20. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin ‘allergy’ in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014; **133**: 790–6
 21. Sadel K, Holtzer Y, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. *Clin Exp Allergy* 2003; **33**: 501–6
 22. Solensky R. Penicillin allergy as a public health measure. *J Allergy Clin Immunol* 2014; **133**: 797–8
 23. Kemp HI, Cook TM, Thomas M, Harper NJN. UK anaesthetists’ perspectives and experiences of severe perioperative anaphylaxis: NAP6 baseline survey. *Br J Anaesth* 2017; **119**: 132–9
 24. Mertes PM, Laxenaire M-C, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003; **99**: 536–45
 25. Baldo BA, Fisher MM, Pham NH. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. *Clin Exp Allergy* 2009; **39**: 325–44
 26. Didier A, Cador D, Bongrand P, et al. Determinants in allergy to muscle relaxants. *J Allergy Clin Immunol* 1987; **79**: 578–84
 27. Johansson SGO, Florvaag E, Öman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. *Allergy* 2010; **65**: 498–502
 28. de Pater G, Florvaag E, Johansson S, Irgens A, Petersen M, Guttormsen A. Six years without pholcodine; Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents. *Allergy* 2017; **72**: 813–9
 29. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2014; **519**: 237–41
 30. Reddy JI, Cooke PJ, Van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. *Anesthesiology* 2015; **122**: 39–45
 31. Sadleir PHM, Clarke RC, Bunning DL, Platt PR, Myles PS. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth* 2013; **110**: 981–7
 32. Laake JH, Rottingen JA. Rocuronium and anaphylaxis—a statistical challenge. *Acta Anaesthesiol Scand* 2001; **45**: 1196–203
 33. Egner W, Cook TM, Harper N, et al. Specialist perioperative allergy clinic services in the UK 2016: results from the Royal College of Anaesthetists Sixth National Audit Project. *Clin Exp Allergy* 2017; **47**: 1318–30
 34. Ebo DG, Bridts CH, Stevens WJ. Anaphylaxis to an urethral lubricant: chlorhexidine as the ‘hidden’ allergen. *Acta Clin Belg* 2004; **59**: 358–60
 35. Krishna M, York M, Chin T, et al. 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
 36. Opstrup M, Malling H, Krøigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy: a large single-centre evaluation. *Allergy* 2014; **69**: 1390–6
 37. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
 38. Garvey LH, Krøigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–15
 39. Nakonechna A, Dore P, Dixon T, et al. Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom. *Allergol Immunopathol (Madr)* 2014; **42**: 44–9
 40. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients—four cases of chlorhexidine allergy. *Acta Anaesthesiol Scand* 2001; **45**: 1290–4
 41. Medicines and Healthcare Products Regulatory Agency. *All medical devices and medical products containing chlorhexidine—risk of anaphylactic reaction due to chlorhexidine allergy*. 2012. <https://www.gov.uk/drug-device-alerts/medical-device-alert-all-medical-devices-and-medicinal-products-containing-chlorhexidine-risk-of-anaphylactic-reaction-due-to-chlorhexidine-allergy>. [Accessed 3 May 2018]
 42. Barthelmes L, Goyal A, Newcombe RG, McNeill F, Mansel RE. Adverse reactions to Patent Blue V dye—the NEW START and ALMANAC experience. *Eur J Surg Oncol* 2010; **36**: 399–403
 43. Brenet O, Lalourcey L, Queinnec M, et al. Hypersensitivity reactions to Patent Blue V in breast cancer surgery: a prospective multicentre study. *Acta Anaesthesiol Scand* 2013; **57**: 106–11
 44. 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
 45. Ishiyama T, Kotoda M, Asano N, et al. The effects of Patent Blue dye on peripheral and cerebral oxyhaemoglobin saturations. *Anaesthesia* 2015; **70**: 429–33

46. Takahashi Y, Hara K, Sata T. A case of prolonged reduction in arterial oxygen saturation measured by pulse oxymetry after administering Patent Blue in an elderly patient. *Masui* 2013; **62**: 422–4
47. Murakami T, Kayo R, Kajita I, Cho S, Saito H. False decrease in pulse oximetry readings due to Patent Blue in a patient with breast cancer. *Masui* 2003; **52**: 909–11
48. Serious Hazards of transfusion (SHOT). <https://www.shotuk.org/>.
49. Ouni B, Bensayed N, Fathallah N, Slim R, Regaieg H. Fatal anaphylactic reaction to intravenous infusion of ondansetron: a report of two cases. *Eur J Anaesthesiol* 2016; **33**: 140–55
50. Asserhøj LL, Mosbech H, Krøigaard M, Garvey LH, Absalom AR. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. *Br J Anaesth* 2016; **116**: 77–82
51. Harper NJN. Propofol and food allergy. *Br J Anaesth* 2016; **116**: 11–3
52. Stewart WJ, McSweeney SM, Kellett MA, Faxon DP, Ryan TJ. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; **70**: 788–92
53. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013; **68**: 1219–32
54. Mahajan RP. Critical incident reporting and learning. *Br J Anaesth* 2010; **105**: 69–75

Handling editor: H.C. Hemmings Jr



Supplementary figure 1 Presenting features of Grade 3-5 perioperative anaphylaxis in female and male patients



Supplementary figure 2. Presenting clinical features and those occurring at any time during clohexidine-induced perioperative anaphylaxis (%).