10 Clinical features

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Key findings

- Perioperative anaphylaxis is a clinical diagnosis, and presenting features may have many other causes that are more common than anaphylaxis. Despite this, early recognition and treatment of anaphylaxis during anaesthesia is key to avoiding harm.
- The proportion of women experiencing anaphylaxis was similar to the proportion of women undergoing anaesthesia and surgery.
- Hypotension was the presenting feature in 46% of cases and occurred during the episode in all cases.
- Hypotension was common in patients with coronary artery disease and those taking beta-blockers or ACE inhibitors. Outcomes in these patients were poor.
- Bronchospasm/high airway pressure was the presenting feature in 18% of cases and occurred in 49% of cases.
- Bronchospasm/high airway pressure was a more common presenting feature in patients with asthma and in obese/morbidly obese patients than in those without these characteristics.
- Urticaria and flushing/non-urticaria rash were uncommon presenting features, even in patients with a past medical history of urticaria.
- Skin signs were uncommon in the more severe cases of anaphylaxis, sometimes only occurring after resuscitation.
- A reduced or absent capnograph trace was reported in only 30% of cases.
- An unrecordably low oximetry recording was associated with severe reactions, especially with respiratory features, and led to prompt treatment by anaesthetists.
- A small number of patients presented with isolated cardiovascular or isolated respiratory features. Anaesthetists should bear this in mind in the early recognition of perioperative anaphylaxis.
- Anaphylaxis presented within 10 minutes of exposure to the culprit agent in 83% of cases. In <2% the presenting feature was delayed beyond 60 minutes.
- NMBA-induced anaphylaxis occurred rapidly. Hypotension was a common presenting feature, particularly with atracurium-induced anaphylaxis, whereas bronchospasm/high airway pressure was more common with suxamethonium-induced anaphylaxis.
- Antibiotic-induced anaphylaxis presented almost uniformly rapidly, and hypotension was the common presenting feature.
- Anaphylaxis caused by chlorhexidine and Patent Blue dye had a rather slower onset: hypotension was the commonest presenting feature and bronchospasm was not seen.

What we already know

Perioperative anaphylactic reactions may lead to substantial morbidity or mortality. Mertes and colleagues reported that 30–60% of anaphylactic reactions are due to IgE-mediated reactions with a 3.5–10% mortality rate (Mertes 2011a; Joint Task Force 2005).

International guidelines on the management of perioperative anaphylaxis emphasise the importance of early recognition and prompt treatment to avoid harm, which can include death or permanent disability (Krøigaard 2007; Harper 2009; Kolawole 2017). As these events occur rarely and randomly, regular education and training of anaesthetists and other members of the theatre team to recognise and treat anaphylaxis is needed (Simons 2014).

The diagnosis of perioperative anaphylaxis is a clinical one, and laboratory tests and biological markers are unhelpful at the time of presentation. A knowledge of the clinical features encountered during anaphylaxis, and a high index of suspicion by the anaesthetist is therefore essential.

Perioperative hypersensitivity reactions involve mainly the cardiovascular, respiratory and muco-cutaneous systems. However, reactions may present with isolated organ system involvement, including any of hypotension, tachycardia, bradycardia, bronchospasm, high airway pressure, oxygen desaturation, cutaneous flushing, urticaria, angioedema, itching, nausea and vomiting, and cardiac arrest (Mertes 2011b, Low 2016).

Clinical features consistent with perioperative anaphylaxis can be readily misinterpreted, as there are numerous possible causes for these signs. These include dose-related side effects of administered drugs, complications of the anaesthetic technique or surgery, and patient co-morbidities as well as hypersensitivity reaction. Unfortunately, the recognition of anaphylaxis is often delayed because key clinical features such as hypotension and bronchospasm more commonly have a non-allergic cause during the perioperative period. For example, severe hypotension after

induction of anaesthesia is not uncommon: clinically important hypotension occurring in 9% of patients within 10 minutes of induction according to one study (Reich 2005). Hypotension also occurs commonly during neuraxial blockade. Bronchospasm may be a more common feature of hypersensitivity in patients with pre-existing asthma, but non-hypersensitivity causes of bronchospasm are considerably more likely during anaesthesia. Widespread flushing or urticaria is seen in some patients with perioperative hypersensitivity reactions, but the absence of cutaneous signs does not exclude anaphylaxis.

The clinical features of perioperative anaphylaxis usually occur within a few minutes of exposure to the allergen, but may be delayed by up to an hour or longer. Reactions to neuromuscular blocking agents and intravenous antibiotics are usually rapid. Conversely, reactions to chlorhexidine, Patent Blue dye and intravenous colloids may be delayed, though this is not universal (Harper *et al* 2009).

Numerical Analysis

Grade of anaphylaxis

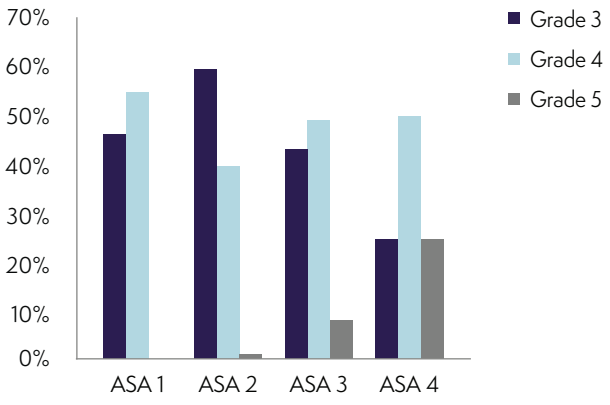
NAP6 inclusion criteria required Grade 3, 4 or 5 perioperative anaphylactic events: Grade 3 anaphylaxis is marked by life-threatening hypotension and/or severe bronchospasm, Grade 4 requires CPR and Grade 5 is fatal (see Chapter 5, Methods).

Grades of all events as determined by the review panel were:

- Grade 3: 136 (51%)
- Grade 4: 120 (45%)
- Grade 5: 10 (3.8%).

Grade 5 reactions were more common in patients with a higher ASA (Figure 1) and this is discussed in Chapter 12, Deaths, cardiac arrest and profound hypotension.

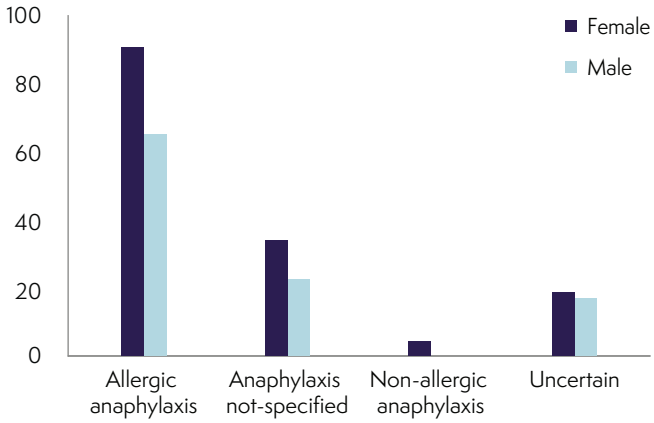
Figure 1. Grade of anaphylaxis and ASA status



Gender

There were more reports of anaphylaxis in women (n=150; 58%) than men (n=108; 42%) (Figure 2), but this matched proportions of women and men undergoing procedures, as measured in the NAP6 Activity Survey (8,965, 58% females and 6,488, 42% males) (Chapter 8, Activity Survey).

Figure 2. Anaphylactic reactions by gender (numbers)

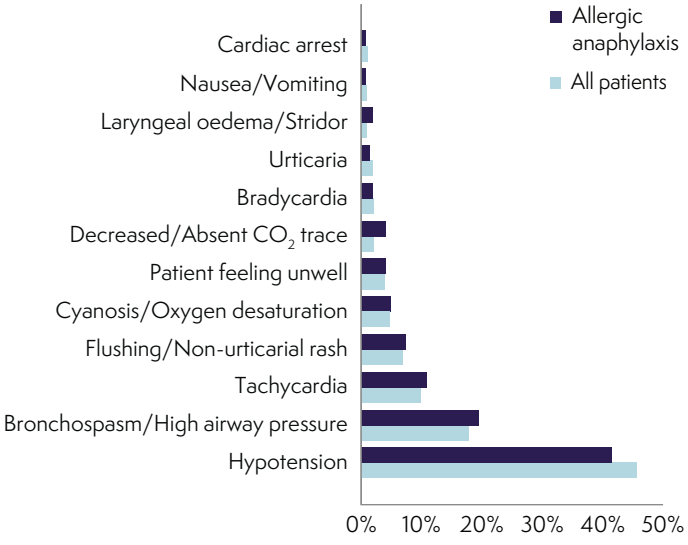


Presenting feature

The commonest presenting feature of perioperative anaphylaxis by far was hypotension (accounting for 46%), followed by bronchospasm/high airway pressure (18%), tachycardia (9.8%), flushing/non-urticarial rash 6.6% and cyanosis/oxygen desaturation (4.7%). A reduced or absent capnography trace was the seventh commonest presenting feature (2.3%). Three patients presented with cardiac arrest (1.2%).

This pattern of presenting feature was very similar in the subgroup of patients subsequently diagnosed as having an allergic anaphylactic reaction (Figure 3). Urticaria was not a common presenting feature or clinical feature during anaphylaxis, even in patients with a history of pre-existing urticaria. This was particularly so in severe cases, and in some cases skin signs only became evident after resuscitation (also see Chapter 12, Deaths, cardiac arrest and profound hypotension).

Figure 3. Presenting features of perioperative anaphylaxis

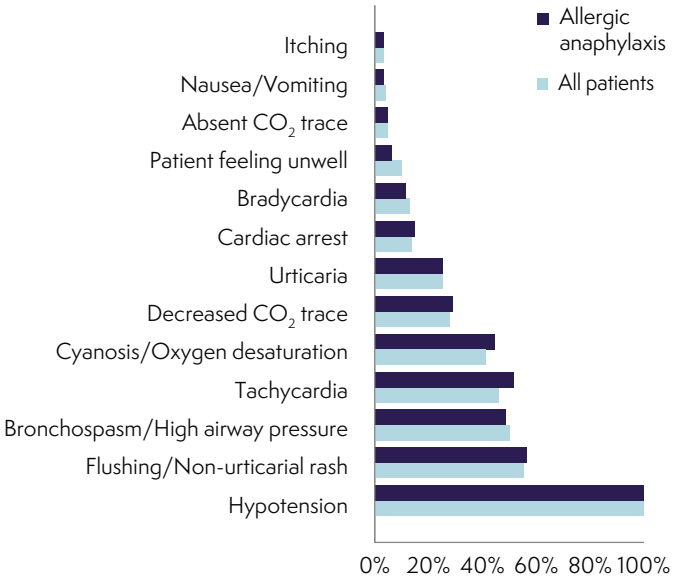


All clinical features during anaphylactic event

Hypotension was also the commonest clinical feature throughout the anaphylactic episode, occurring in all patients. This was followed by flushing/non-urticarial rash in 56%, bronchospasm/high airway pressure in 49%, tachycardia in 46%, cyanosis/oxygen desaturation in 41% and a reduced or absent capnograph trace in 30%. Again, this clinical pattern was very similar in the subgroup of allergic anaphylaxis patients (Figure 4).

A healthy patient scheduled for elective day-case surgery, became hypotensive (systolic blood pressure <50 mmHg) with reduced capnography trace and oxygen desaturation within five minutes of induction. Over the next 20 minutes the patient received multiple doses of metaraminol, followed by a metaraminol infusion and also boluses of ephedrine before the possibility of anaphylaxis was considered and treated with adrenaline. No flushing of urticarial rash was seen at any point during the event. Subsequent investigations confirmed allergic anaphylaxis.

Figure 4. Clinical features present at any time during an episode of perioperative anaphylaxis



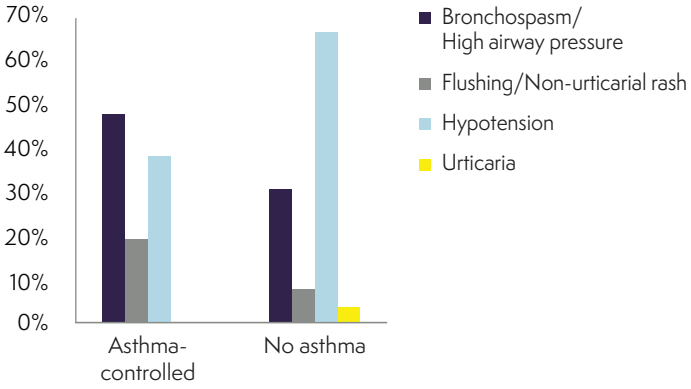
Isolated organ system involvement

Fifteen (5.6%) patients presented with isolated cardiovascular features and four (1.5%) with isolated respiratory features.

History of asthma

In patients with a history of asthma, bronchospasm/high airway pressures were proportionately more common, both as first presenting features and as clinical features occurring at any point during the anaphylaxis episode (Figure 5). This was true even when the condition was well controlled preoperatively.

Figure 5. Presenting features of perioperative anaphylaxis in patients with and without asthma



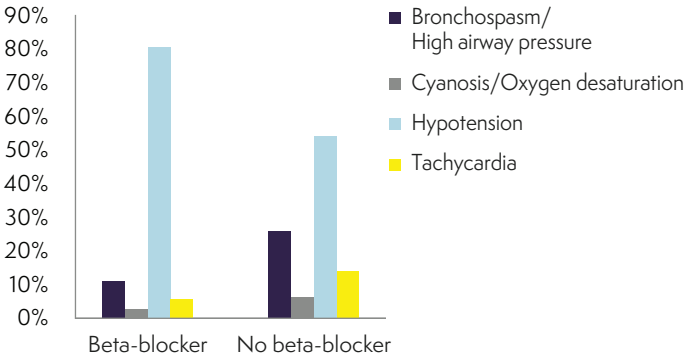
History of coronary artery disease

In contrast to asthma, there was no important difference in first presenting feature or clinical features during the anaphylactic episode in patients with or without a history of coronary artery disease. However, patients with coronary artery disease were more likely to experience fatal events (see Chapter 12).

Patients taking beta-blockers

Tachycardia was infrequent in these patients, either as a presenting feature or as one occurring during the episode (Figure 6). Bronchospasm was also proportionately less likely to occur during the event. These patients generally had higher-grade events and this is discussed in Chapter 12.

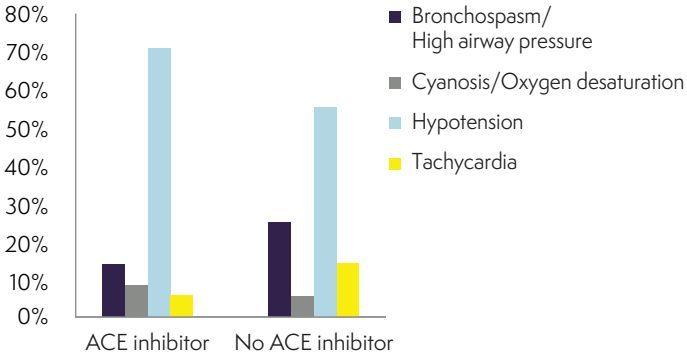
Figure 6. Presenting features in patients taking beta-blocker medication



Patients taking an ACE inhibitor

In patients taking an ACE inhibitor, hypotension was a main presenting feature and was common during anaphylaxis (Figure 7). These patients generally had higher-grade events, and this is discussed in Chapter 12.

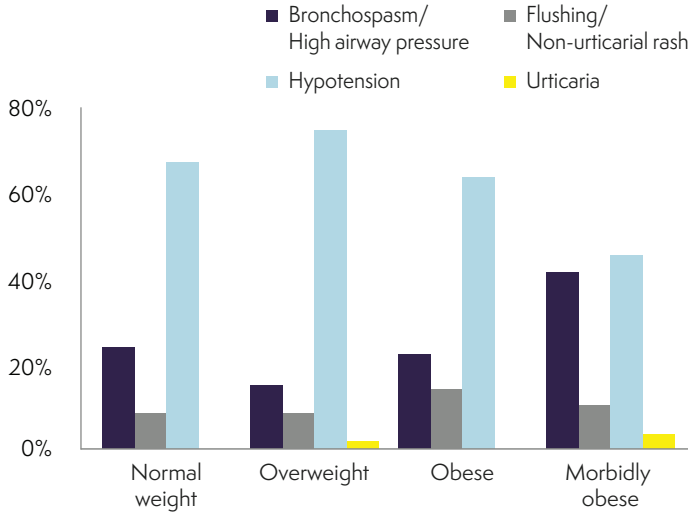
Figure 7. Presenting features in patients taking ACE inhibitor medication



Body habitus

Bronchospasm and high airway pressure was the presenting feature in 34% of obese and morbidly obese patients, and 15% of non-obese patients (Figure 8).

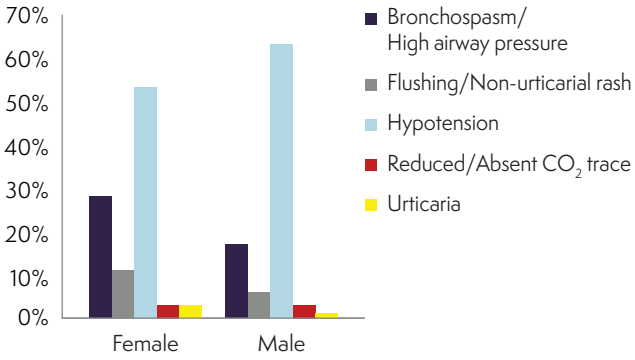
Figure 8. Presenting features according to body habitus



Influence of gender on presenting feature

In terms of presenting features, hypotension was slightly more common in men and bronchospasm slightly more common in women (Figure 9). This may be explained by differences between the genders in rates of coronary artery disease (men 23.7% vs women 8.4%) and use of beta-blockers and ACEI medication (26.7% vs 11.2% and 21.2% vs 15.2% respectively), whereas more women than men had asthma (25% vs 15.5%). Similar proportions of either gender were obese (38% vs 39%).

Figure 9. Presenting features of perioperative anaphylaxis in male and female patients



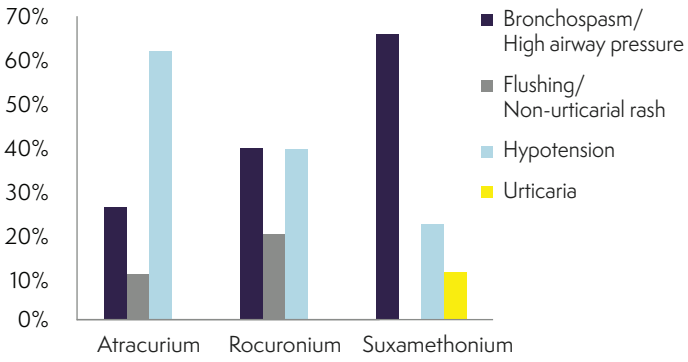
Culprit Agent

Neuromuscular blocking agents (NMBAs)

Although the numbers were small, we noted differences in the presenting features amongst different NMBAs responsible for anaphylaxis: atracurium was more commonly associated with hypotension and suxamethonium with bronchospasm/high airway pressure. Rocuronium was associated with both bronchospasm and hypotension in approximately equal measure (Figure 10).

However, taking all clinical features that occurred during anaphylaxis into account, the commonest clinical feature was hypotension for all three NMBAs.

Figure 10. Presenting features of NMBA anaphylaxis

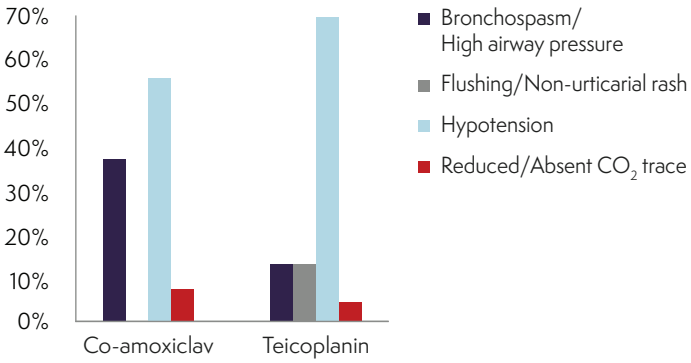


Amongst patients with anaphylaxis to NMBAs, women were relatively over-represented: 46 women and 19 men.

Antibiotics

Cardiovascular features (hypotension and tachycardia) were the predominant presenting features in patients with antibiotic-induced anaphylaxis. During teicoplanin anaphylaxis, hypotension was a dominant presenting feature with bronchospasm uncommon (Figure 11).

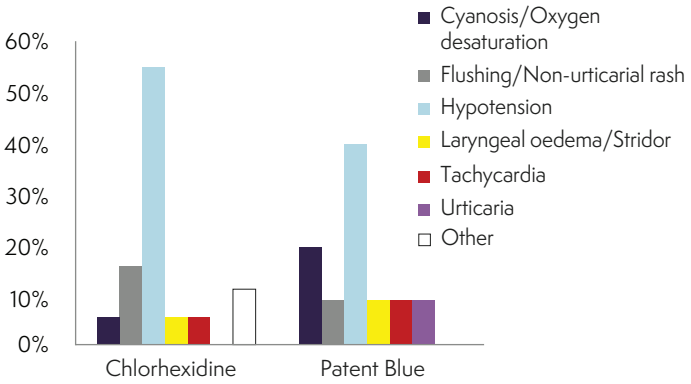
Figure 11. Presenting features of co-amoxiclav and teicoplanin anaphylaxis



Chlorhexidine and Patent Blue dye

Hypotension was the commonest presenting feature in chlorhexidine and Patent Blue anaphylaxis (Figure 12). Of 18 patients with chlorhexidine anaphylaxis, there were 15 men and two women (gender not specified for one patient). All patients with Patent Blue dye anaphylaxis were women undergoing breast or gynaecological surgery.

Figure 12. Presenting features of chlorhexidine and Patent Blue anaphylaxis



Time from exposure to presenting feature

In the majority of anaphylactic events (83%), the presenting feature appeared within 10 minutes of exposure to the culprit agent.

In only 5 cases (1.9%) was appearance of the presenting feature delayed beyond 60 minutes (Table 1).

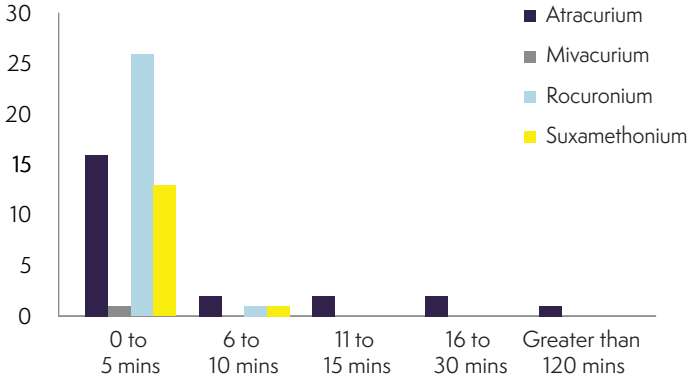
Table 1. Time from exposure to presenting feature

Time from exposure to presenting feature	Number (percentage) of patients
0 - 5 mins	176 (66.2%)
6 - 10 mins	44 (16.5%)
11 - 15 mins	13 (4.9%)
16 - 30 mins	19 (7.1%)
31 - 60 mins	7 (2.6%)
61 - 120 mins	3 (1.1%)
>120 mins	2 (0.75%)
Blank	2

Time from exposure to presenting feature by culprit agent

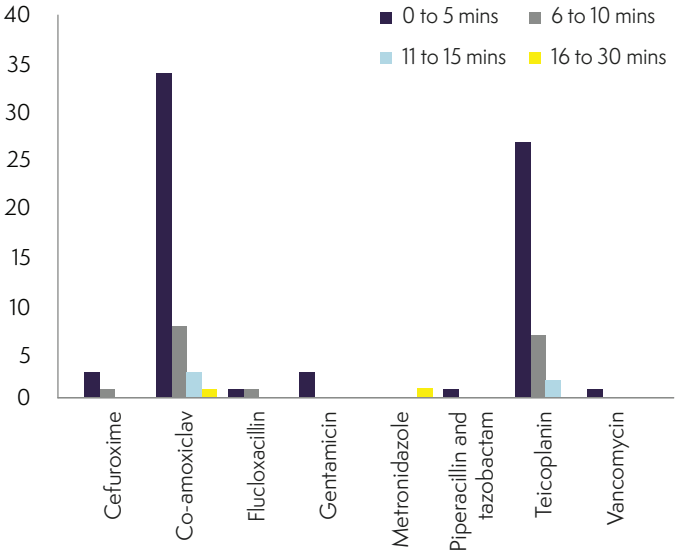
When the culprit agent was an NMBA presentation was rapid, in all but one case (98%) presentation occurred in <30 minutes, and for all cases related to rocuronium, suxamethonium and mivacurium (Figure 13) presentation was in <10 minutes. An isolated case of atracurium anaphylaxis presenting at >120 minutes after exposure may have been a data-entry error.

Figure 13. Time from exposure to presentation: NMBA-induced anaphylaxis



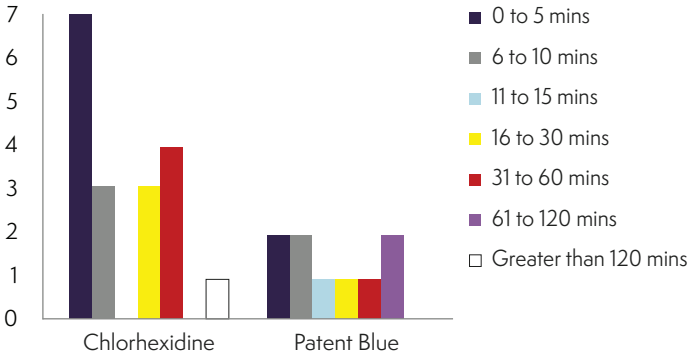
Similarly, when the culprit agent was an antibiotic, the presenting feature occurred rapidly – in <15 minutes in 97% of cases and in <30 minutes in all cases. (Figure 14).

Figure 14. Time from exposure to presentation: antibiotic-induced anaphylaxis



Some slower reactions were seen when the culprit agent was chlorhexidine or Patent Blue dye, frequently at >10 minutes and some at >120 minutes (Figure 15), and in reactions to orally administered drugs.

Figure 15. Time from exposure to presentation: chlorhexidine and Patent Blue dye induced anaphylaxis



Time to suspect and treat anaphylaxis

The time interval between exposure to the suspected agent and the anaesthetist suspecting and treating anaphylaxis is reported in Chapter 11, Immediate management. Here we note that speed of response may vary according to presenting feature. Response was always <10 minutes when the presenting feature was cardiac arrest, bradycardia, reduced/absent capnograph trace, and laryngeal oedema. However, longer delays (up to 60 minutes) occurred when the presenting feature was hypotension, bronchospasm/high airway pressure, cyanosis/oxygen desaturation, non-specific flushing, and reports of an awake patient feeling unwell.

Reduced capnography trace and grade of reaction

During the anaphylactic event, a reduced or absent capnograph trace was recorded in 80 (30%) of 266 cases. There was no clear correlation with grade of reaction (Table 2).

Table 2. Patients with reduced capnograph trace and grade of reaction

Grade of reaction	All patients n=266	Patients with reduced or absent capnograph trace. n=80	Percentage of cases in that grade
3	136	34	25%
4	120	43	36%
5	10	3	30%

Unrecordably low oxygen saturation

A total of 31 cases reported an unrecordably low oxygen saturation at some point during the anaphylactic event. When compared to the entire group of patients with anaphylaxis, this subgroup of patients were more likely to experience a Grade 4 or 5 reaction. These patients were also more likely to exhibit respiratory features or cardiac arrest/profound hypotension. This group of patients tended to have rapid onset anaphylaxis (exposure to presentation <5 minutes in 84%), and anaesthetists were prompt in suspecting and treating anaphylaxis.

Discussion

Several publications have suggested that a higher proportion of perioperative anaphylactic reactions occur in women, possibly related to sex hormones (Mertes 2003; Harboe 2005; Chen 2008; Leysen 2013). Our data indicate that the higher number of female patients with perioperative anaphylaxis was proportional to the higher number of female patients undergoing surgery and anaesthesia in general. Nevertheless, subgroup analyses revealed twice as many women as men when the culprit agent was an NMBA and a preponderance of male patients when the culprit agent was chlorhexidine. This is consistent with published data to date (Light 2006; Egner 2017) although differences in gender-based baseline exposure to these triggering agents is unclear.

Under-diagnosis of anaphylaxis is common, especially when there is a lack of cutaneous involvement in presentation. Our data indicate that although presenting features may vary, hypotension is universal during perioperative anaphylaxis (see also Chapter 12, Death, cardiac arrest and profound hypotension). Unexplained perioperative hypotension should prompt anaesthetists to consider anaphylaxis as a differential diagnosis in this setting. Muco-cutaneous signs are often absent at presentation, particularly in the more severe events.

It is well recognised that perioperative anaphylaxis can present as isolated organ system involvement and this was seen in a small minority of patients, even amongst the cohort of Grade 3 to 5 reactions that were the subject of NAP6. Other features such as itching, urticarial rash, or tissue swelling may be absent or masked either by general anaesthesia or as a consequence of the severity of the reaction (see also Chapter 12, Death, cardiac arrest and profound hypotension). Anaesthetists must therefore exercise a high index of suspicion in recognising perioperative anaphylaxis, as not all patients present with the 'full-blown' picture with involvement of the cardiovascular, respiratory and muco-cutaneous systems.

We noted some differing patterns in presentation depending on the trigger agent and patient co-morbidities. Amongst the NMBAs, hypotension was the commonest presenting feature in atracurium anaphylaxis, and bronchospasm/high airway pressure in suxamethonium anaphylaxis. Hypotension was also the commonest presenting feature in anaphylaxis due to chlorhexidine, Patent Blue dye and antimicrobials. As expected, hypotension was a common presenting clinical feature in patients taking beta-blockers or ACE inhibitors.

In the vast majority of cases, and for most culprit agents, presentation was within 10 minutes of exposure. This might be expected, as almost all drugs are delivered intravenously in the perioperative setting. The exceptions to this were chlorhexidine and Patent Blue dye, where presentation was more likely to be modestly (>10 minutes) or significantly (>30 minutes) delayed. This was also observed in reactions to drugs administered orally. This delay is probably due to the time lag in absorption of the allergen through skin, mucosal surfaces and/or soft tissues, and this is discussed further in Chapter 17, Chlorhexidine and Chapter 18 Patent Blue dye.

Some clinical features are clearly of immediate concern to the anaesthetist or are often associated with anaphylaxis, and these appeared to prompt the anaesthetist to suspect anaphylaxis and to start anaphylaxis-specific treatment swiftly. These clinical features included cardiac arrest, reduced or absent capnograph trace, and laryngeal oedema. Other clinical features, in particular hypotension, occur relatively frequently during anaesthesia, and causes unrelated to anaphylaxis are far more common: these confounding issues may cause a delay in the recognition and treatment of anaphylaxis. Though perioperative anaphylaxis is relatively rare, it should be high in the differential diagnosis of unexplained or severe hypotension during anaesthesia. Considering the diagnosis is the first step to recognising it.

Although bronchospasm and high airway pressures are commonly associated with exacerbation of asthma or airway stimulation, it may be a presenting feature of anaphylaxis and this is particularly the case in patients with pre-existing asthma, including patients with pre-existing good control. Assuming that all bronchospasm in asthmatics is caused by poor asthma control risks delaying or missing a diagnosis of anaphylaxis. Anaesthetists should therefore exercise caution in attributing bronchospasm or high airway pressures in the perioperative period solely to exacerbation of asthma.

A recent publication suggested that an end-tidal carbon dioxide value below 2.6 kPa is a useful independent marker of a severe anaphylactic reaction (Gouel-Cheron 2017). Capnography is readily and continuously measured throughout routine general anaesthesia, and a sudden reduction in the end-tidal carbon dioxide concentration could prompt early diagnosis and management of anaphylaxis. The NAP6 data, from cases of severe anaphylaxis, has not strongly confirmed this finding. While we did not ask reporters to report end-tidal carbon dioxide values, we did ask whether a reduced or absent capnograph trace was present. This was only reported in 30% of all patients. Whether this casts doubt on the previous findings or indicates failure to recognise or report this change is uncertain. Further examination of this observation is merited but it has not been confirmed in this study.

We found that patients who had an unrecordably low oxygen saturation at some point during the anaphylactic event experienced severe reactions. These cases were severe reactions with either prominent respiratory features or cardiac arrest/ profound hypotension. These cases were recognised and managed promptly by the anaesthetist, and this may be a useful sign in recognising severe anaphylaxis.

Our data indicate that patients with higher ASA, with a history of coronary artery disease and those taking beta-blocker medication or ACE inhibitors were more likely to have profound hypotension and poor outcomes – this is discussed further in Chapter 12, Deaths, cardiac arrest and profound hypotension. Vasopressin and glucagon were rarely administered in this setting, and this is discussed in Chapter 11, Immediate management and departmental organisation.

Recommendations

Institutional

- All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements.

Individual

- Perioperative anaphylaxis can present with a single clinical feature, in particular isolated hypotension. Anaesthetists should exercise a high index of suspicion in recognising perioperative anaphylaxis and commence treatment promptly
- In patients with asthma, the occurrence of bronchospasm or high airway pressures should not automatically be attributed to acute asthma, as, in these patients this may be the presenting feature of life-threatening anaphylaxis
- As anaphylaxis may be delayed, particularly with some oral drugs, referrals to allergy clinics should include details of all agents that the patient has been exposed to within at least the previous 120 minutes
- During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1 mg should be considered, repeated as necessary.

Research

- Further studies are required to clarify the role of a fall in end-tidal carbon dioxide concentration in the early recognition and management of severe perioperative anaphylactic reactions
- The role of glucagon and vasopressin in refractory anaphylaxis (particularly in high risk groups such as the elderly, and those taking beta blockers or ACE inhibitors) needs further investigation.

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