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Identification of factors affecting the outcome of General Anaesthetic Allergy Testing

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To the Editor,

Allergic reactions are a rare complication of anaesthesia and anaphylaxis is estimated to affect 1 in every 10,000 anaesthetics in the UK. Investigating reactions can be complex due to the frequent absence of validated skin tests to commonly implicated items, the large number of drugs given during surgery and the presence of non-IgE mediated reactions.

Identification of allergies by giving test doses during subsequent surgery is inappropriate in the case of Neuromuscular Blocking Agents (NMBAs) and in general clinicians rely on validated skin tests to identify the culprit as well as potential cross reactivity with other NMBAs. Choosing the right drug concentrations for skin testing is not straightforward and different concentrations have been promoted for each drug¹. Very high concentrations result in irritant reactions, leading to false positives. With too low a concentration, the sensitivity is diminished and the causative agent may not be identified. Although most centres follow standardised guidance, skin tests have not been validated for many drugs used during surgery such as Ondansetron, Nonsteroidal anti-inflammatory drugs (NSAIDs) and certain antibiotics.

It is therefore not surprising that in a third of cases a causative agent is not found². We aimed to describe the range of presentations seen at our General Anaesthetic Allergy testing service and identify differences

in those with or without a causative agent identified. We did this by performing a retrospective analysis of patients who had undergone general anaesthetic allergy testing at the Bart's Allergy Service during the 4 year period from 2014 to 2017.

The electronic notes for these patients were accessed and the referral letters, referral proformas, anaesthetic charts and medical notes were analysed for details of the original reaction. The referral proforma used by our centre was based on one from the Association of Anaesthetists of Great Britain and Ireland (AAGBI). The signs of the reaction, the drugs given before the reaction (implicated agents) and the treatments were recorded. Results of skin testing, drug provocation tests and IgE tests were also recorded along with advice given to patients and details of any subsequent reaction.

Serum Specific IgE tests were performed to agents including penicillin V, penicillin G, amoxicilloyl, chlorhexidine and suxamethonium when indicated. Skin testing had been performed according to established guidelines³⁻⁵. Skin Prick and Intradermal test concentrations used are noted in Supplemental Data 1. Serum tryptase had been determined using the ImmunoCAP® platform (Phadia). When indicated, graded drug provocation tests had been carried out in an outpatient challenge unit. All testing was guided by the history and referral information. In cases where a patient tested positive to an implicated agent, this was noted as the "causative agent." In a minority of cases, the patient was positive to more than 1 implicated agent and these were all noted as causative for the purposes of the analysis.

The statistical significance of the differences in tryptase rise between those with and without a causative agent was calculated using a Welch's t-test due to the unequal sample sizes between the groups.

Statistical significance between proportions of patients with various signs and treatments was calculated using a Chi-Squared test. R studio© version 1.2.1335 was used for statistical analyses.

A total of 42 cases were analysed; 22 male and 20 female patients. The average age was 52.9 years.

Causative agents were established in 62% of cases investigated but they could not be established in the remaining 38%. The most commonly used implicated medications were propofol and fentanyl, however, NMBA's were responsible for the majority of the reactions (43%), followed by antibiotics (17%), (Figure 1). The frequency of signs and treatments are shown in the Supplemental Data 2 and 3 respectively.

We attempted to identify why no causative agent was found in 38% of cases. We first analysed the tryptase results of investigated patients. Serial Tryptase measurements were recorded in only 23 of 42 patients (54%). In these patients, we calculated the difference between the highest and lowest measurements which we termed the “tryptase rise”. The mean tryptase rise in those with and without a causative agent found was 39 µg/L and 3.4 µg/L respectively ($p=0.045$), (Figure 2). We then looked at the differences in reported signs between the two groups (Supplemental Data 4). Only the proportion of patients with hypotension were statistically different between those with and without a causative agent found (73% vs 25% respectively, $p<0.001$). There was no statistical difference between the proportion of patients receiving various treatments between the two groups (Supplemental Data 5).

We also noted whether any investigated patients had an allergic reaction during subsequent surgery. We found only one such case involving a 79-year-old gentleman who was initially referred to us with an episode of anaphylaxis at the start of coronary artery bypass surgery. We identified an allergy to chlorhexidine but unfortunately, when the patient was readmitted for a second attempt, he had another episode of anaphylaxis following insertion of a urinary catheter that was not recognised as being impregnated with chlorhexidine. There was no case of anaphylaxis to an agent not identified on testing.

Many national and international allergy organisations report that a causative agent will not be identifiable in a third of the cases and our data was in broad agreement with this². The reasons for negative tests could be poor sensitivity, inaccurate referral information or the absence of an IgE mediated process.

All our patients with a causative agent had either hypotension or a rise in tryptase. Of those without a causative agent, 75% did not have either hypotension or a rise in tryptase. Considering that patients with no identifiable causative agent had a significantly lower average tryptase rise and were less likely to suffer hypotension (compared with those with an identifiable causative agent), our data suggests that an IgE mediated reaction did not take place in these patients. In addition, our data suggests that the sensitivity of allergy skin tests are high. Certainly, if the tests had too low a sensitivity, we would not have expected the differences in tryptase rise seen between the 2 groups.

The National Audit Project 6 (NAP 6) study⁶ found that hypotension was the most common sign in patients with grade 3 to 5 anaphylaxis. Our study (which also includes grade 1 and 2 reactions) corroborates this finding.

Anaesthetic Allergy Guidelines detailing testing protocols are widely used. However, management of those for whom a causative agent is not found is lacking. In this situation, clinicians can be left in a difficult situation. In addition, provocations are impractical in the case of NMBAs and Propofol. Our study suggests that clinicians should expect that a causative agent is unlikely to be identified when there is no significant rise in tryptase or hypotension. However, a referral to a tertiary referral centre should still be made to investigate this further³.

There are several reasons why a causative agent may not be identified. Firstly, it may be felt that a reaction is multifactorial. For example, a minor non-IgE mediated reaction (such as NMBAs activating the MRGPRX2 receptor) may be exacerbated by cofactors, resulting in a severe systemic reaction⁷.

Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) is an important cofactor. NSAIDs increase leukotriene production by inhibiting cyclooxygenase⁸.

Use of beta blockers and angiotensin-converting enzyme inhibitors also augment allergic reactions by promoting the activation of mast cells through interaction with FcεR1⁹. Exercise and menstruation are also commonly known cofactors.

In some cases, no causative agent is found if the reaction was due to a side effect. It is known that several drugs such as NMBAs can cause bronchospasm in a non-IgE dependant manner. No causative agents were identified and no rise in tryptase levels were seen in the 3 cases where only bronchospasm was given as a sign.

Serum Tryptase has a proven role in identifying IgE mediated reactions during general anaesthesia.

However, previous analyses of sensitivity and specificity vary on how IgE mediated reactions are defined.

A French study found a sensitivity and specificity of 64% and 89% respectively when all cases where a positive test implicated a culprit were identified as IgE mediated². A British multi-centre study found a sensitivity and specificity of 63.9% and 73.7% respectively but excluded reactions thought to be non-IgE mediated based on the details from the history¹⁰. The tryptase assay itself has limitations and is known to return false negative results with suboptimal sample handling.

The quality of our data has the following limitations. Firstly, completed referral forms were available in only 31% of cases due to a less strict adherence to referral criteria at the start of the analyses. In addition, the timing of signs were not analysed as the referral data often did not contain this information. This could have helped us separate suspected immediate and delayed type reactions.

Another important observation was suboptimal understanding of serial tryptase measurements by the referrers. Only 23 (55%) had serial measurements, leaving 7 (17%) patients with only a single tryptase result.

Another limitation is that in some cases patients tested positive to two or more implicated agents and hence multiple causative agents were noted. Although it is unlikely for a patient to have reacted to more than one agent, drug provocation testing to determine the single causative agent would have been risky and often a pragmatic approach to avoid all agents with positive tests was taken.

Our findings may have an important implication for screening of referrals as we found that we are unlikely to find a causative drug in reactions with an absence of hypotension or tryptase rise. This finding needs to be corroborated by a second study with more complete tryptase measurements.

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Ethics Statement

This was a retrospective study and involved no active intervention. Therefore, no ethical approval was required.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to the inclusion of patient identifiable information.

Declaration of interest

None

Author Contribution

SB and EZ carried out the data collection. CM, AM, PP and FRA treated and investigated the patients. SB and FRA drafted the manuscript.

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Figure 1

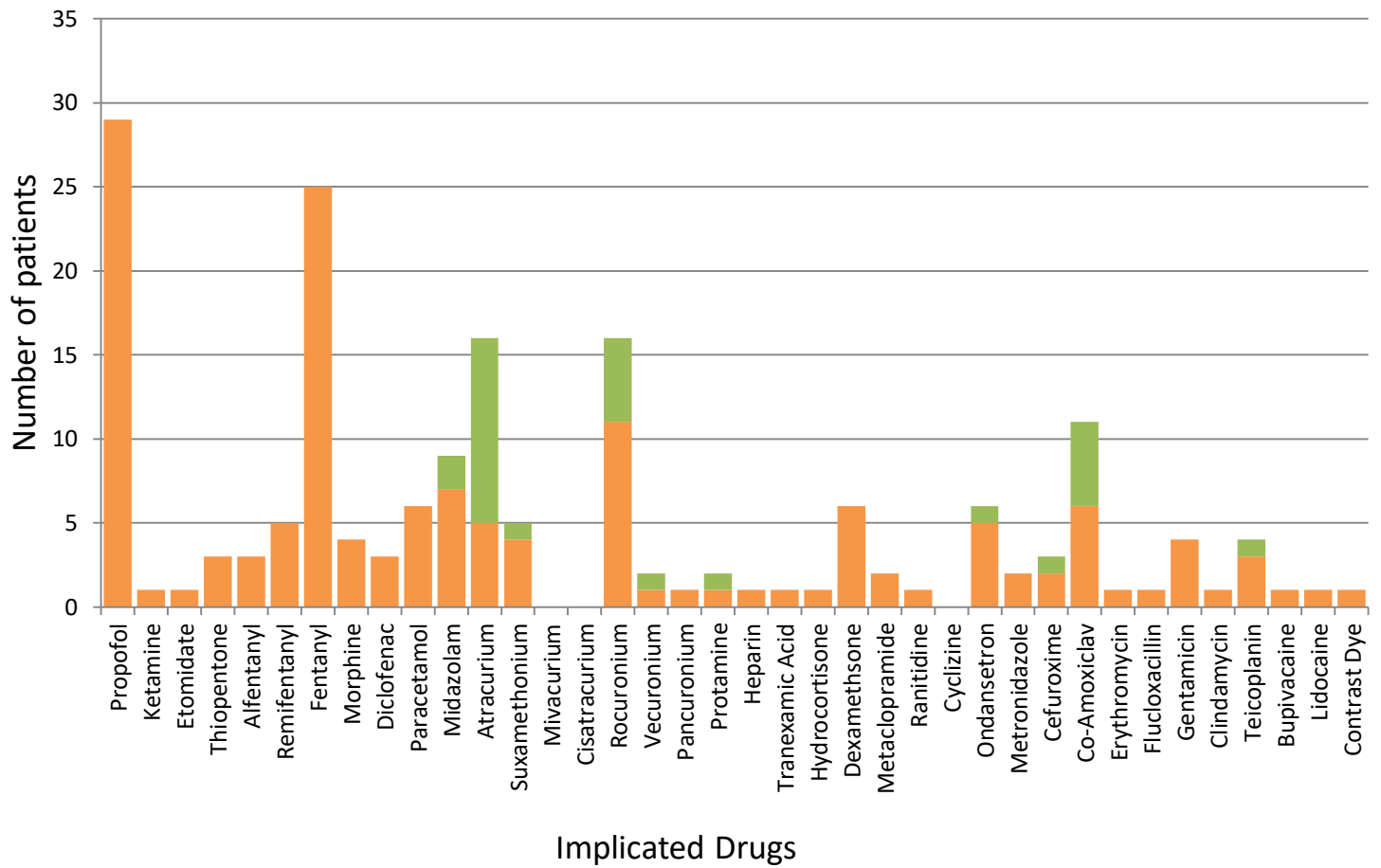


Figure 1: Frequency of medications administered before the reaction. Causative agents are shown in green and non-causative agents are shown in orange.

Figure 2

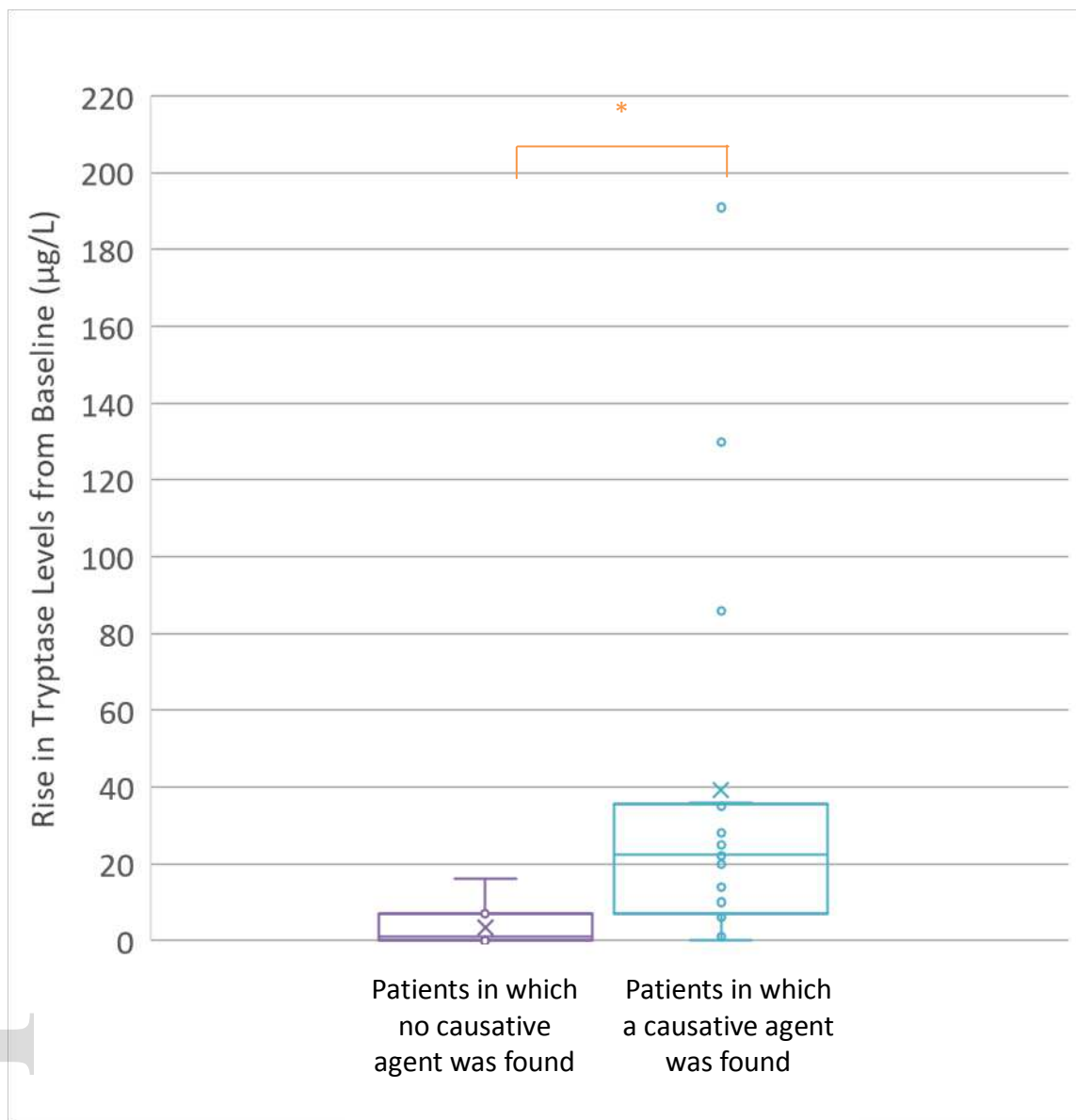
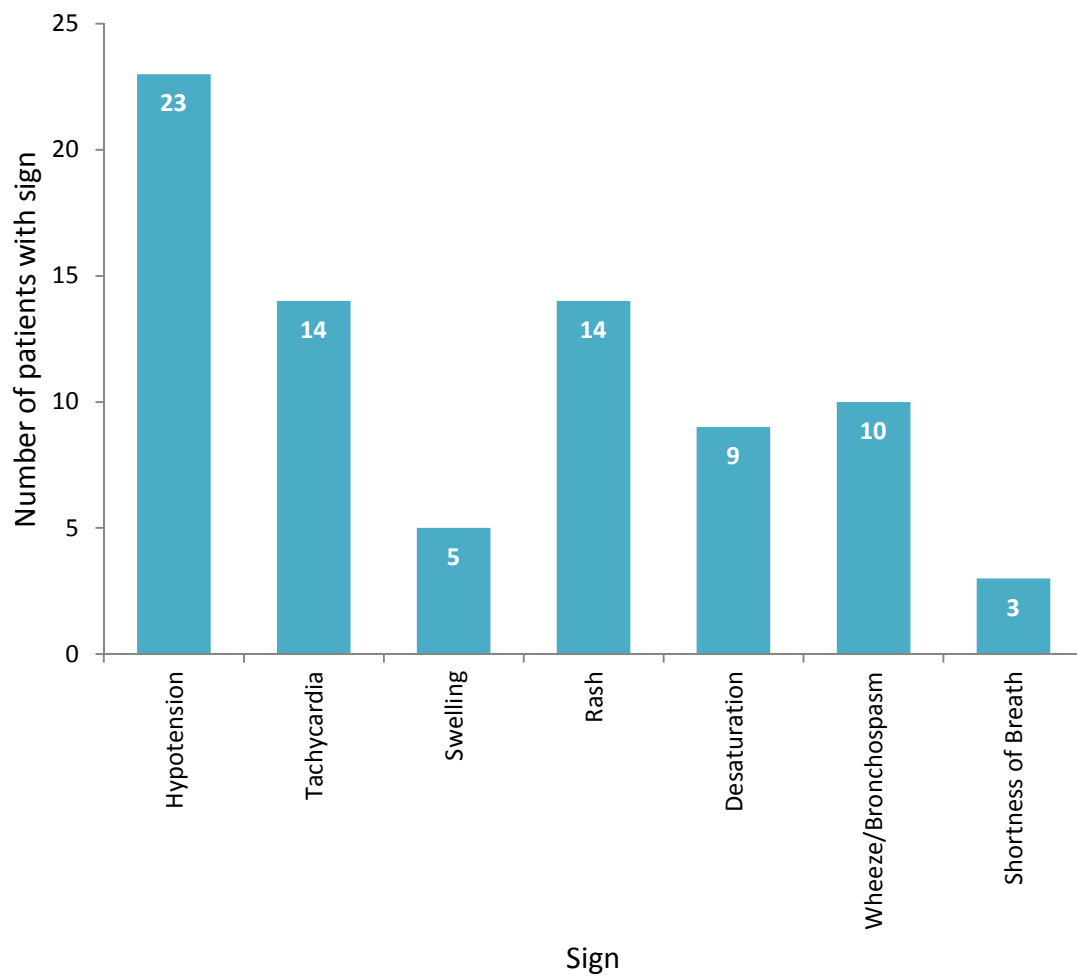


Figure 2: Rise in Tryptase levels in those patients with (mean 39 µg/L, (n=16)), and without (mean: 3.4 µg/L, (n=7)) a causative agent identified. A statistical difference was found between these two groups (p=0.045)

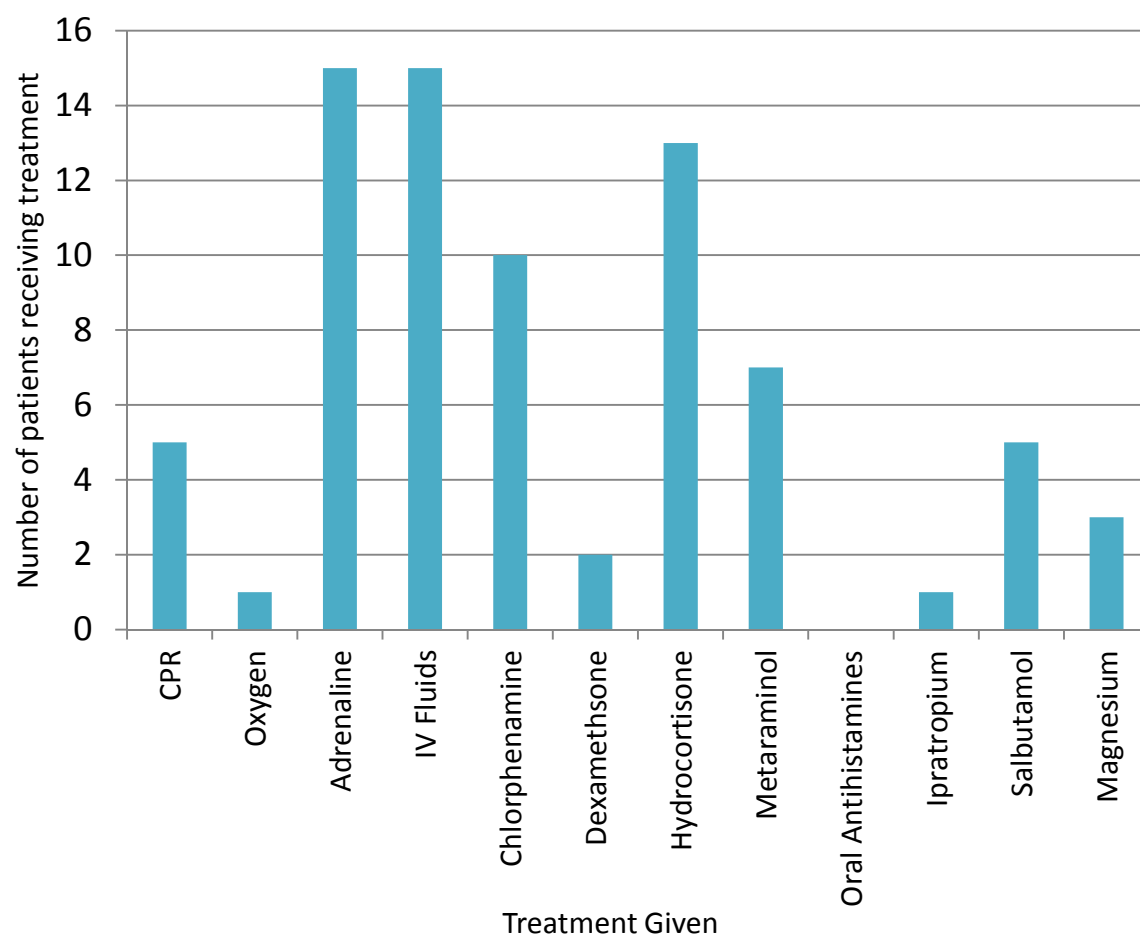
Supplemental Data

Drug	Skin Prick Test Concentration Used	Intradermal Test Concentration
Propofol	10 mg/mL	1 mg/mL
Ketamine	10 mg/mL	1 mg/mL
Etomidate	2 mg/mL	0.2 mg/mL
Thiopentone	25 mg/mL	2.5 mg/mL
Alfentanyl	0.5 mg/mL	0.05 mg/mL
Remifentanyl	0.05 mg/mL	0.005 mg/mL
Fentanyl	0.05 mg/mL	0.005 mg/mL
Morphine	1 mg/mL	0.01 mg/mL
Midazolam	5 mg/mL	0.5 mg/mL
Atracurium	1 mg/mL	0.01 mg/mL
Suxamethonium	10 mg/mL	0.1 mg/mL
Mivacurium	0.2 mg/mL	0.002 mg/mL
Cisatracurium	2 mg/mL	0.02 mg/mL
Rocuronium	10 mg/mL	0.05 mg/mL
Vecuronium	4 mg/mL	0.4 mg/mL
Pancuronium	2 mg/mL	0.2 mg/mL
Protamine	10 mg/mL	0.01 mg/mL
Heparin	1,000 IU/mL	100 IU/mL
Dexamethasone	0.4 mg/mL	0.4 mg/mL
Ondansetron	2 mg/mL	0.02 mg/mL
Metronidazole	2 mg/mL	0.02 mg/mL
Cefuroxime	2 mg/mL	2 mg/mL
Penicilloyl-poly-L-lysine (Penicillin allergy testing)	5×10^{-5} mM	5×10^{-5} mM
Minor determinant mixture (Penicillin allergy testing)	2×10^{-2} mM	2×10^{-2} mM
Co-Amoxiclav	30 mg/mL	30 mg/mL
Gentamicin	40 mg/mL	4 mg/mL
Teicoplanin	20 mg/mL	2 mg/mL
Bupivacaine	2.5 mg/mL	0.25 mg/mL
Lidocaine	20 mg/mL	2 mg/mL
Chlorhexidine	5 mg/mL	0.002 mg/mL

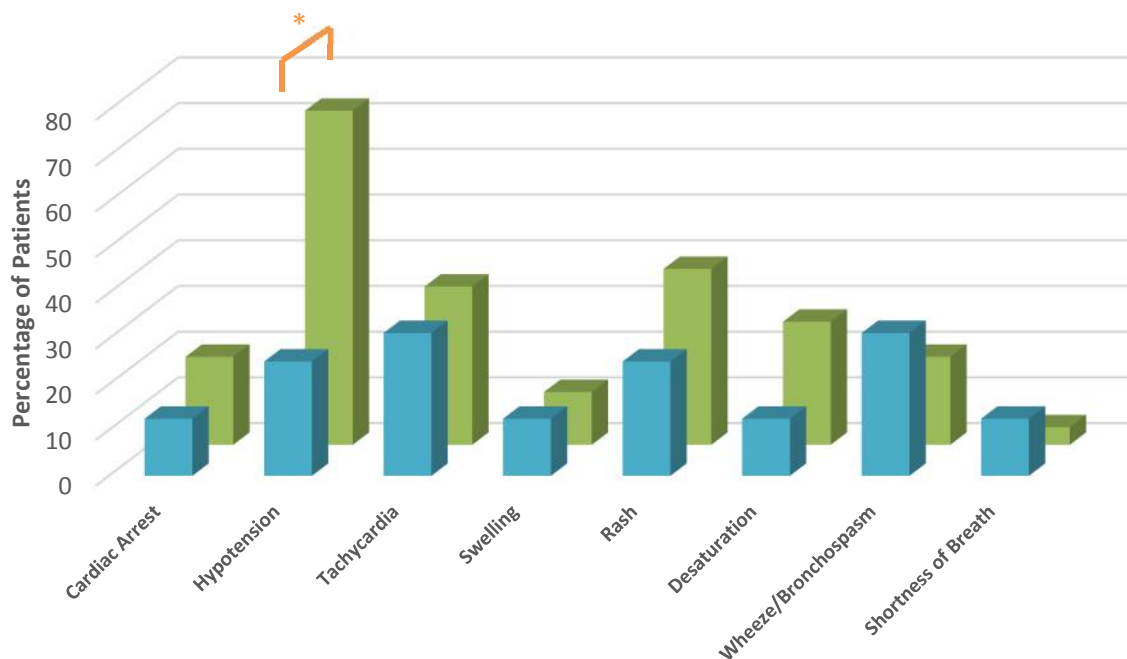
Supplemental Data 1: Skin prick and intradermal test concentrations used in testing patients with suspected anaesthetic allergy



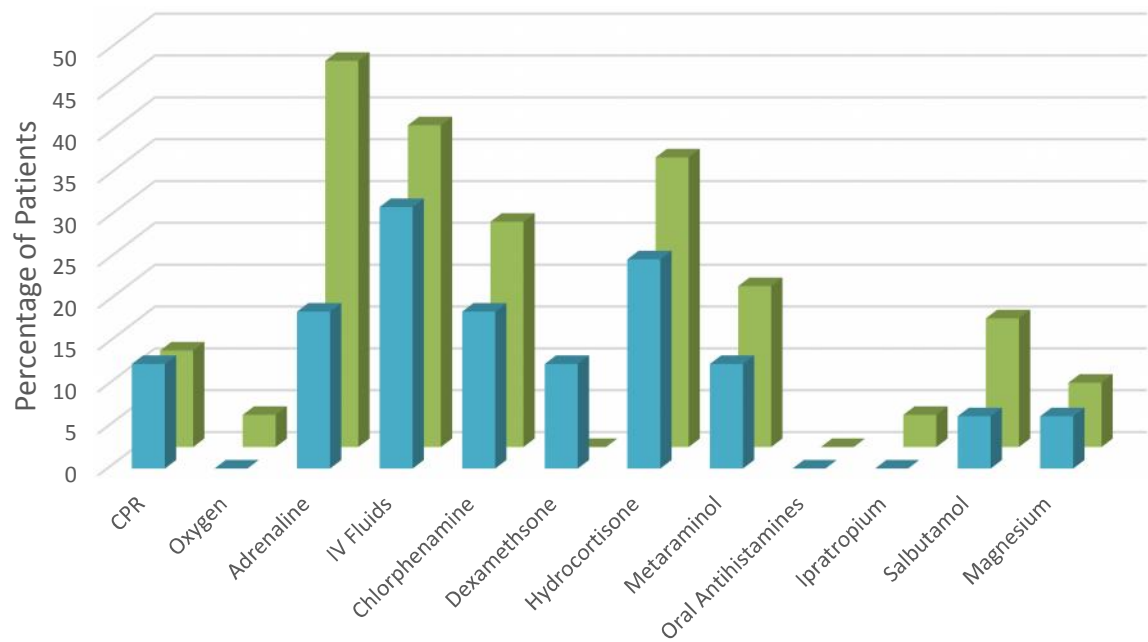
Supplemental Data 2: Frequency of signs occurring with suspected cases of anaesthetic allergy.



Supplemental Data 3: Frequency of Treatments received by patients.



Supplemental Data 4: Frequency of Signs recorded in those with (green) and without (blue) a subsequent causative agent identified. *There was a statistically significant difference in the percentage of patients experiencing hypotension between the 2 groups ($p < 0.001$)



Supplemental Data 5: Percentage of patients receiving various treatments in those with (green bars) and without (blue bars) a subsequent causative agent identified. No statistically significant difference was found between the 2 groups.