

Timing of skin testing after a suspected anaphylactic reaction during anaesthesia

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Background: A delay of 4 to 6 weeks after a suspected anaphylactic reaction has commonly been recommended before performing skin testing. However, sometimes surgery cannot be delayed, and investigation must be done earlier. Recent recommendations suggest that skin testing can be performed immediately after a reaction.

Methods: We describe three cases in which skin testing was performed within 3 weeks after the suspected anaphylactic reaction. A literature review was undertaken to evaluate cases where skin testing was performed within 3 weeks of a suspected anaphylactic reaction during anaesthesia.

Results: Review of the literature did not give a definite answer

to the optimal timing of skin testing after a suspected anaphylactic reaction during anaesthesia.

Conclusions: Only positive skin tests can be taken into account, and there is little safety data to provide confidence in early skin testing. A protocol of how to act if urgent surgery is necessary is suggested.

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MOST of the allerge-anaesthetic literature recommend a delay of 4 to 6 weeks after an anaphylactic reaction prior to skin testing.^{1–6} Recently, it was stated by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Society for Allergy and Clinical Immunology (BSACI) that this delay was unnecessary, and testing could be carried out immediately after a reaction.^{7,8} This would have particular benefit when an operation is abandoned because of anaphylaxis but still needs to be performed urgently.

We describe three cases in which skin testing was performed within 3 weeks after the suspected anaphylactic reaction and review the literature to assess the role of immediate skin testing.

Methods

Articles were identified by a PUBMED search using the terms *anaphylaxis*, *anaesthesia* and *skin test* (from 1964 to January 2011) and *anaphylaxis*, *anaesthesia* and *review* (from 2002 to January 2011). In each article, we paid special attention to the timing of skin testing in relation to the suspected anaphylactic reaction, the reason for this timing and the correlating references. The number of articles was reduced

on the basis of title and abstract. Articles were then divided to review articles, studies and case reports (less than 10 patients).

Results

Case reports

Case 1. A 68-year-old man was anaesthetized with propofol, sufentanil and rocuronium for a mediastinoscopy to stage a spinocellular carcinoma of the lung. After intubation, ventilation was impossible, and pulse oximetry failed to give a reading. A generalized rash and urticaria developed. Blood pressure decreased to 46/31 mmHg without changes in heart rate. End-tidal CO₂ fell to 1.3 kPa. The man was treated with boluses of adrenaline intravenously (i.v.) (up to 1.1 mg) followed by a continuous infusion, colloids, and methylprednisolone, ranitidine, promethazine and phenylephrine i.v. Surgery was cancelled. He was extubated 3 h later. Mast cell tryptase (MCT) was 37 µg/l 1 h after the start of the reaction (normal value < 13.5 µg/l).

Because of the relative urgency of the pathology, skin testing was done 4 days after the acute event. The tests showed a clear sensitivity to rocuronium

and succinylcholine [positive skin prick tests (SPTs) undiluted] and vecuronium [mildly positive SPT undiluted, but positive intradermal test (IDT) at 10^{-3} dilution]. Tests for cisatracurium, mivacurium and latex were negative. Baseline MCT was $2.1 \mu\text{g/l}$.

One week after the initial reaction, the patient was anaesthetized for a mediastinoscopy, followed by a thoracotomy, with propofol, sufentanil and cisatracurium. No reaction occurred.

Case 2. A 71-year-old man had several perioperative anaphylactic reactions during previous surgeries. During surgery for implantation of a knee prosthesis, he had an episode of 'hypotension, bronchial hypersecretion and generalized erythema', which was treated symptomatically. An indwelling urinary catheter (IDC) had been inserted, presumably using lignocaine 2% and chlorhexidine 0.05%. The diagnosis of anaphylaxis was not made.

Due to infection, debridement of his knee wound was uneventfully performed twice without an IDC. He then required revision of his prosthesis. The morning following the first-stage revision of his knee prosthesis, he had a change of IDC. He immediately developed erythema and cardiovascular collapse requiring cardiopulmonary resuscitation, adrenaline and hydrocortisone i.v., and colloids. Latex was suspected in history, but IDT and radioallergosorbent test (RAST) were negative.

After an uneventful induction of anaesthesia for a second-stage revision of his knee prosthesis, he became tachycardic and hypotensive and developed a generalized urticaria shortly after insertion of an IDC using lignocaine 2% and chlorhexidine 0.05% and prepping the skin with 2% chlorhexidine in alcohol. He was treated successfully with adrenaline and hydrocortisone i.v., and colloids. MCT was $26.1 \mu\text{g/l}$ immediately after the event and $15.8 \mu\text{g/l}$ at 6 h. SPTs performed 6 days later were negative for chlorhexidine and lignocaine. Eleven weeks later, IDTs for all anaesthetics were negative, but SPT (undiluted) and IDT (10^{-4} dilution) were strongly positive for chlorhexidine. He had two uneventful general anaesthetics, omitting chlorhexidine.

Case 3. A 71-year-old man underwent anaesthesia for a laparoscopic hemicolectomy for a caecal carcinoma. After induction of anaesthesia with midazolam, fentanyl, propofol and rocuronium, he immediately developed tachycardia, hypotension, bronchospasm and skin flushing. The reaction was treated with boluses of adrenaline i.v. (up to 0.150 mg), followed by a continuous infusion. The

case was cancelled. MCT was $114 \mu\text{g/l}$ at 1 h and $4.4 \mu\text{g/l}$ at 24 h.

Twenty days after the reaction, IDTs for all drugs used as well as for other neuromuscular blockers were negative even at concentrations 10 times stronger. Only a SPT to rocuronium was slightly suspicious (only mild erythema).

He was retested at 6 weeks and 5 days. Only skin tests to rocuronium were strongly positive (IDT at 10^{-2} dilution; SPT undiluted). The anaesthesia for the hemicolectomy was uneventful using cisatracurium.

Literature review

The PUBMED search, using the terms anaphylaxis, anaesthesia and skin test, retrieved 287 articles; the second PUBMED search, using the terms anaphylaxis, anaesthesia and review, 80, from which, respectively, 107 and 20 articles were selected: 25 review articles, 46 studies and 56 case reports.

We did not find a study performing skin testing before 3 weeks or comparing skin testing at different times after the suspected anaphylactic reaction during anaesthesia.

We found two studies specifically investigating the timing of skin testing. Frick et al. measured concentrations of histamine in guinea-pigs after anaphylatoxin treatment and concluded that '*after histamine depletion, there is a slow biosynthesis of histamine, a considerable time being required for the tissue histamine to return to its control value. . . . The slow rise in pulmonary histamine after 2 1/2 weeks coincides with the return of anaphylactic susceptibility.*'⁹ Goldberg determined the best time for venom skin tests after insect-sting anaphylaxis.¹⁰ Thirty-five patients had skin tests during the first week after the suspected anaphylactic reaction and also 4 to 6 weeks later. Two patients reacted only during the first week and 15 patients only after 4 to 6 weeks; 18 patients reacted at both times. Goldberg concluded that there was a fourfold decrease in sensitivity of skin tests immediately after the sting; this was in contrast to immunoglobulin E (IgE) sensitivity, which was better during the first week.

The case reports performing skin tests before 3 weeks are summarized in Table 1. We excluded four cases because high concentrations of the suspected drugs were used during IDT, or questionable conclusions were made.¹¹⁻¹⁴ In six case reports (eight patients), a positive skin test to a substance was found between 3 and 14 days after the suspected anaphylactic reaction.¹⁵⁻²⁰

In three case reports, skin testing was negative shortly after the anaphylactic reaction and became

Table 1

Case reports performing skin testing before 3 weeks.

Author	Drugs used before suspected anaphylactic reaction	ST performed before 3 weeks		ST performed later than 3 weeks	
Russ BR ¹⁵	IDC using chlorhexidine	2 days	SPT chlorhexidine +		N.D.
Sprung J ¹⁶	Propofol, vecuronium, fentanyl, isosulfan blue	10 days	SPT isosulfan blue +		N.D.
Kubitz JC ¹⁷	Etomidate, sufentanil, rocuronium	3 days	IDT rocuronium 1 : 1000 +		N.D.
Yang YL ¹⁸	Propofol, lignocaine, fentanyl, cisatracurium	14 days	IDT cisatracurium 1 : 1000 +		N.D.
Hunting AS ¹⁹	Propofol, remifentanyl, patent blue	14 days	SPT patent blue +		N.D.
	Propofol, remifentanyl, patent blue	14 days	SPT patent blue +		N.D.
Newman MJ ²⁰	Propofol, fentanyl, patent blue	14 days	SPT patent blue +		N.D.
	Succinylcholine (occupational)	3 days	IDT succinylcholine 1 : 100 +	4 weeks	IDT rocuronium 1 : 100 + IDT vecuronium 1 : 100 + IDT pancuronium 1 : 100 + IDT d-tubocurare 1 : 1000 +
Fisher MM ²¹ (patient 3)	Thiopental, succinylcholine, d-tubocurare	4 days	IDT all –	3 weeks	
Aalto-Korte K ²²	Natural rubber latex	12 days	SPT natural rubber latex –	3 months	SPT natural rubber latex +
Culp JA ²³	Cefazolin	6 days	IDT and SPT cefazolin –	6 weeks	SPT cefazolin +

IDC, indwelling urinary catheter; ST, skin test; IDT, intradermal skin test; SPT: skin prick test; –, negative; +, positive; N.D., not done.

positive at a later time. In the first case report,²¹ after induction of anaesthesia with thiopentone, succinylcholine and d-tubocurare, a 42-year-old woman was difficult to ventilate and quickly became cyanosed and pulseless. IDT after 4 days was negative, but was positive after 3 weeks to d-tubocurare. In the second case report,²² a 58-year-old woman developed oedema and swelling of her face, a sense of laryngeal swelling and hypotension during a vaginal ultrasound examination; the probe had a natural rubber latex (NRL) cover. Twelve days after the suspected anaphylactic reaction, the SPT was negative to NRL. Three months later, the patient had a positive SPT to NRL. The SPT to histamine was positive and the same in size at both times. The authors explained this by suggesting specific desensitization of the skin mast cells to NRL. In the third case report,²³ a 44-year-old man had an anaphylactic reaction during anaesthesia 1 min after the injection of cefazolin. Skin testing for cefazolin was negative after 6 days, but positive after 6 weeks.

Discussion

In our case reports and the review of the literature, we did not find a definite answer to the optimal timing of skin testing after a suspected anaphylactic reaction during anaesthesia.

The culprit of the anaphylactic reaction during anaesthesia is not evident because the patient comes into contact with multiple intravenous drugs and

different substances (e.g. latex, disinfectants) in a short time span. As a consequence, there is a high degree of error if anaesthetists make guesses about the likely causative agent.²⁴ Investigation is necessary to determine the causative agent and consists of MCT and post-operative tests.^{1,3,25}

A positive MCT supports an IgE-mediated cause.⁵ The timing of MCT is clear: a minimum of two samples, the first 60–90 min after the start of the reaction and the second at least 24 h later to determine a baseline value.^{6–8}

Post-operative tests are for specific IgEs and/or skin tests. These tests look for the responsible drug and examine cross-sensitivity between muscle relaxants if the responsible drug is a muscle relaxant.⁵ Specific IgEs can be determined at the time of the reaction as there is no consumption of circulating IgE antibodies during anaphylaxis.^{2,26} This is in contrast with IgG antibodies which are consumed in immune complexes during an allergic reaction (e.g. dextran) and thus disappear from the circulation.²⁶ However, specific IgE tests have a low sensitivity and specificity and are only available for a limited number of drugs, and as a consequence, one cannot determine cross-sensitivity between muscle relaxants with as much precision as with skin testing.^{4,6–8,27}

Skin tests are the best-studied diagnostic tests after a suspected anaphylactic reaction during anaesthesia. Most experts advise to postpone skin testing 4 to 6 weeks after the reaction.^{1–6} If skin testing is done earlier, only positive skin tests can be taken into

account.^{25,28–30} Our case reports and the review of the literature seem to suggest that early skin testing can result in more false-negative skin tests. A study testing the same patients at different time points after a reaction during anaesthesia has not been done yet.

Some authorities acknowledge this lack of data about the optimal time interval to perform skin tests.^{26,31,32} In contrast, two recently published guidelines of the AAGBI and the BSACI state that there is no reason to delay skin testing after an allergic reaction, and that it may be performed as soon as the patient has recovered from the reaction and from the effects of the drugs used to treat anaphylaxis.^{7,8} The previous guideline of the AAGBI in 2003 advised a delay of 4 to 6 weeks, but the reason for the change in the more recent guideline is not given.*

In most patients, surgery can be postponed 4 to 6 weeks until the results of the skin tests are available, but sometimes, surgery is more urgent and the abandoned operation needs to be performed without delay. The drug responsible cannot usually be reliably determined without investigation. Although most anaphylactic reactions are due to intravenous anaesthetics, especially muscle relaxants, about 30% are caused by antibiotics and latex.³³ Moreover, guessing the culprit is wrong in 70% of the cases in one study.²⁴ Completely avoiding the drugs used is not safe either due to the high incidence of cross-sensitivity between muscle relaxants and also between penicillins and cephalosporins.^{3,4,7,8}

Table 2 suggests a protocol of how to act if urgent surgery is needed. Preparations should be made to treat an anaphylactic reaction.⁵ A latex-free environment should be created, and penicillins and cephalosporins should be avoided if used during the suspected anaphylactic reaction.^{5,7,27,29,34} Use an antiseptic not used in the suspected anaphylactic reaction (chlorhexidine or povidone iodine).^{5,7} If available, specific IgEs can be determined, but results should be interpreted with caution, given their imperfect sensitivity and specificity. There are several options for anaesthesia depending on whether muscle relaxation is needed if it was used in the original reaction. In many cases, all anaesthetics can be completely avoided by using inhalation or regional anaesthesia.^{5,6,27,29,34}

If muscle relaxation is necessary, skin testing must be performed, but the results of negative skin tests need to be interpreted with caution, as is illustrated

Table 2

Suggested protocol if urgent surgery is needed.

1. Be prepared to treat an anaphylactic reaction.
 2. Avoid latex.
 3. Avoid penicillins and cephalosporins if used.
 4. Switch to the other antiseptic (chlorhexidine or povidone iodine).
 5. If available, determine specific IgEs, but interpret with caution.
 6. Use a different technique (avoiding all drugs used during the suspected anaphylactic reaction):
 - a. Regional anaesthesia.
 - b. Inhalation anaesthesia.
 7. Use of a different technique is not possible (muscle relaxation needed): 'early' skin testing:
 - a. Positive
 1. Use skin test-negative drugs.
 2. Use a muscle relaxant of different chemical structure (benzylisoquinolinium or aminosteroid structure).
 - b. Negative
 1. Pre-treatment with antihistamines and steroids?
 2. Use a muscle relaxant of different chemical structure (benzylisoquinolinium or aminosteroid structure).
 3. Progressive challenge if high-risk drug unavoidable.
-

by our second and third case and the literature.^{21–23,30} Only positive results can be taken into account.^{25,28–30}

If skin testing is positive for a muscle relaxant, the use of a muscle relaxant that tested negative and has a different chemical structure (benzylisoquinolinium or aminosteroid structure) is advised.^{8,35} Pre-treatment with corticosteroids and histamine H₁-receptor antagonists reduces the incidence of non-IgE-mediated anaphylactic reactions, but this is not proven for anaphylactic reactions.^{5,7,27,29} There is little data on the use of challenge or small i.v. test doses, but anaphylactic reactions are reported after intradermal skin testing with small amounts of very diluted drugs.^{7,27} Progressive challenge with increasing doses may be acceptable if anaesthesia cannot be delayed, safe alternatives cannot be found, and a 'high-risk' drug is not avoidable. For neuromuscular blockers, pancuronium and cisatracurium have the lowest incidence of anaphylaxis.²⁷

Conclusion

Skin testing is best performed 4 to 6 weeks after a suspected anaphylactic reaction. If results are needed earlier, only positive skin tests can be taken into account, and there is little safety data to provide confidence in early skin testing. The value of a negative skin test as well as the results of cross-sensitivity between muscle relaxants need to be interpreted with caution. Studies comparing skin testing early after the suspected anaphylactic reaction and 4 to 6 weeks later are needed.

*Suspected anaphylactic reactions associated with anaesthesia, Revised edition. 2003; <http://www.aagbi.org/sites/default/files/anaphylaxis03.pdf> [Accessed 22 January 2011].

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