

What investigation after an anaphylactic reaction during anaesthesia?

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Purpose of review

Anaphylactic reactions occurring during anaesthesia may be life threatening. Lethal issues may be involved in up to 3–10% of the cases. The allergological assessment (including biochemical tests and skin tests) is the key to the management of these reactions. The scope of this review is to focus on the allergological assessment required to prove the immune mechanism, to identify the culprit drug or substance and the cross-reactive molecules, especially for neuromuscular blocking agents, allowing preventive measures for future anaesthetic procedures.

Recent findings

To describe the allergological assessment (including biochemical tests and skin tests performed according to the current guidelines) in order to prove the immune mechanism as the responsibility of the culprit allergen. The most frequent and less frequent drugs involved are described. The different biological tools available are detailed. To ensure an accurate diagnosis, the interpretation of the allergological assessment should be linked to the description of the clinical events as their time onset following the injection/administration of the suspected drug(s)/substance.

Summary

To describe the different tools (biochemical tests and skin tests) available in order to prove the diagnosis of an anaphylactic reaction occurring during anaesthesia.

Keywords

anaesthesia, anaphylaxis, hypersensitivity, immediate, skin tests, tryptase

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Introduction

Anaphylaxis is a clinical syndrome involving multiple organ systems, most commonly the skin, the cardiovascular and respiratory systems. During the perioperative period, a lethal issue might be involved in up to 3–10% of the cases [1,2]. Follow-up allergological investigation should therefore be performed after the occurrence of a perioperative immediate hypersensitivity reaction to ascertain an accurate diagnosis in order to prevent a further re-exposure of the culprit allergen. The scope of this review is to focus on the allergological assessment required to prove the immune mechanism, to identify the culprit drug or substance and the cross-reactive molecules, especially for neuromuscular blocking agents (NMBAs), allowing preventive measures for future anaesthetic procedures.

Epidemiology of perioperative anaphylaxis

The incidence of anaphylaxis occurring during anaesthesia has been estimated between one in 10 000 and one in 20 000 in Australia [3] and at one in 13 000 in France [4]. The estimated frequency of anaphylactic reactions is of one in 6500 and of one in 5200 general anaesthesias in

which NMBAs were administered, in France and in Norway, respectively [4,5]. Nevertheless, the exact incidence remains underestimated. The morbidity of these reactions is unknown. Recently, anaphylaxis was considered to be involved in 3% of the deaths totally or partially related to anaesthesia in France [2], whereas 10% of anaesthesia-related immediate hypersensitivity reactions reported to the UK Medicines Control Agency are fatal [1]. Nevertheless, about 60% of the immediate hypersensitivity reactions occurring during anaesthesia are IgE mediated. NMBAs are the most common causative agents involved followed by latex and antibiotics [6,7]. In contrast, in a limited number of patients experiencing adverse reactions during anaesthesia, latex was the first agent involved [8].

Clinical history of perioperative anaphylaxis

The initial diagnosis of perioperative anaphylaxis is only presumptive and based on the clinical signs described (Table 1) [9], the onset delay between the introduction of the suspected allergen and the occurrence of the clinical signs as the treatment of the reaction. Clinical symptoms associated with an anaphylactic reaction are variable, both

Table 1 Clinical severity scale of immediate reactions^a

Grades	Clinical signs
I	Skin symptoms and/or mild fever reaction
II	Measurable but not life threatening Cardiovascular reaction (tachycardia, hypotension) Gastrointestinal disturbances (nausea)
III	Respiratory disturbances Shock
IV	Life-threatening bronchospasm Cardiac arrest

^a According to Ring and Messmer [9].

in their features and severity. During anaesthesia, the reported clinical features, associated or not, are cardiovascular symptoms, bronchospasm and cutaneous–mucous signs. The most severe reactions may involve only one system, most commonly the cardiovascular system, such as cardiovascular collapse or cardiac arrest [10[•]].

Anaphylactic reactions may occur at any time during the perioperative period, but are mostly observed early after induction of anaesthesia, within minutes or seconds after the injection of the responsible drug. In contrast, latex or agents administered via other routes (patent blue, chlorhexidine, etc.) may induce reactions which are usually delayed, that is 30–60 min after the beginning of the surgical procedure or their injection/application. Such reactions might also occur immediately [11]. Follow-up investigations (including biochemical tests and skin tests) are required to identify the mechanism of these immediate hypersensitivity reactions occurring during anaesthesia and the culprit allergen in order to avoid a potentially life-threatening re-exposure of the patient to the attending drug/substance [11,12,13[•]]. Nevertheless, the interpretation of the biological results and/or skin tests performed should be linked to the description of the clinical events as their time onset following the injection/administration of the suspected drug(s)/substance to ensure an accurate diagnosis.

Allergological assessment

Allergological assessment include biochemical tests and skin tests.

Biochemical tests

Biochemical tests are available, either *in vivo* or *in vitro*.

In-vivo biochemical tests

Early increased plasma histamine confirms the *in-vivo* histamine release. Histamine concentrations in plasma can be reliably measured by immunoassay. During allergic reactions to drugs, histamine concentrations are immediately maximal and decrease thereafter with a half-life of about 20 min [14]. False negative values have

been identified during pregnancy, plasma histamine being metabolized by diamine oxidase released by the placenta [12]. Tryptase concentrations, measured in serum by immunoassay, reach a peak between 15 min and 1 h and decrease slowly, with a half-life of 90 min [14]. An increase of histamine concentrations indicates activation of mast cells and/or basophils, whereas an increase of tryptase is specific for mast cell activation, as basophils have low tryptase levels. Histamine and tryptase measurements have been recommended for the diagnosis of allergic reactions during anaesthesia [12], whereas others only recommend tryptase measurements [1,6[•],13[•]].

In-vitro biochemical tests

In-vitro tests available in clinical practice detect the presence of IgE antibodies by the radioallergosorbent test (RAST). The presence of specific IgEs of NMBAs in serum has been initially demonstrated using NMBA coupled to epoxy-sepharose (Cap-RAST). The sensitivity of this test, however, is limited and therefore was improved by coupling an analogue of choline to sepharose (quaternary ammonium sépharose or QAS) [15], or *p*-aminophenylphosphoryl-choline (PAPPC) on agarose [16]. A morphine-based solid phase IgE assay was also proposed to diagnose anaphylaxis to NMBAs as common antigens were involved [17]. These *in-vitro* tests may help to confirm the diagnosis in patients experiencing an anaphylactic reaction to NMBAs or to identify the culprit drug in patients who cannot be skin tested. Placing the tested serum in the presence of the soluble form of the culprit molecule controls the inhibition of specific IgE binding. The concordance rate with skin tests is about 80% in most cases [12].

The RAST test available for latex is less sensitive than the skin prick test (PT) with latex, being positive only in 50–70% of the cases [11]. The indications for specific IgE assays are currently restricted to the diagnosis of anaphylaxis to NMBAs, thiopental and latex [12].

Several other tests have been proposed for indirect detection of specific IgE to anaesthetic drugs. The basophile histamine release test is reliable for NMBAs, its sensitivity is about 40–100% according to the different studies, whereas its specificity is 98–100% [12]. This technique might be required when cross-reactivity among NMBAs is investigated for re-introduction of NMBAs in patients having presented a documented anaphylaxis to NMBAs [12]. The study of basophil activation in the presence of the allergen is assessed by the expression of CD63 on the plasma membrane using flow cytometry. Its sensitivity and specificity are estimated to be around 60 and 90%, respectively [6[•]]. Nevertheless, further investigations are needed to assess the value of this method in the diagnosis of anaphylaxis to NMBAs.

Skin tests

Skin tests remain the gold standard for the detection of IgE-mediated reactions by exposing the mast cells of the skin to the suspected allergen.

Procedure: when, how, to whom?

Skin tests have to be applied according to the suspected pathomechanism of the hypersensitivity reaction. Immediate hypersensitivity reactions should therefore only be investigated by immediate reading skin tests after 15–20 min. Skin tests should be preferentially performed after a delay of 4–6 weeks after the reaction because of mast cell depletion and in order to avoid false negative tests. When they are carried out earlier, a risk of false negative results cannot be discarded and only positive skin tests should be considered relevant. Except for latex sensitization in which groups at risk are well defined, there is no role for systematic preoperative screening in the general population, one does not know the predictive value of skin tests for the occurrence of perioperative anaphylaxis [6[•],12].

Skin test reactivity should be first verified by negative (saline solution) control test [prick test or intradermal test (IDT), using an equal volume of the solvent] and a positive control test (prick test or IDT using an extract of 9% codeine phosphate solution and a 10 mg/ml solution of histamine) that produces a wheal with a diameter of at least 3 mm at 20 min.

A prick test is considered positive if, within 15 min of injecting the allergen solution on the forearm, a wheal

equal to at least half the positive control and larger than the negative control appears. The IDT is performed on the patient's back or on the forearm by injecting 0.02–0.03 ml of the drug at a diluted concentration ranging from 10^{-4} to the pure solution, raising a wheal of about 3 mm. The IDT is considered positive if within 15–20 min after injection, an erythematous and pruriginous wheal appears surrounded by a flare, at least doubling the size of the injection wheal.

Skin tests must include latex and all drugs injected just before the reaction in order to respect the chronology of the event. Investigation of anaesthetic agents is performed by prick tests and/or IDTs [1,6[•],12] using commercial solutions undiluted or diluted in aqueous phenol [12]. All drug dilutions must be freshly prepared under sterile conditions. In France, the different concentrations of anaesthetic agents normally nonreactive in practice of skin tests have been recommended (Table 2) [12]. If no reaction can be elicited by the prick test, IDTs are first realized with a 1/1000 dilution of the agent, except with NMBAs and morphine for which a 1/10 000 dilution is recommended. When the first IDT is negative, then successive 10-fold lower dilution is used with a 15–20 min interval between each IDT without exceeding the maximal concentration. In contrast, if the prick test is very positive, no IDT will be performed or with a 1/100 000 dilution. The drug concentrations as the diagnostic criteria stated by the French Society of Anaesthesiology and Intensive Care Medicine [12] are recommended to be used by Scandinavians [13[•]] or have been adapted by others [6[•]].

Table 2 Concentrations of anaesthetic agents normally nonreactive during skin tests

Drugs		Prick tests		IDTs	
INN	C (mg/ml)	Dilution	Maximal concentration (mg/ml)	Dilution	Maximal concentration (μg/ml)
Atracurium	10	1/10	1	1/1000	10
Cis-atracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0.2	1/1000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/100	100
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1000
Thiopental	25	Undiluted	25	1/10	2500
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	1/10	0.05	1/10	5
Morphine	10	Undiluted	1	1/1000	10
Remifentanil	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1000
Mepivacaine	10	Undiluted	10	1/10	1000
Ropivacaine	2	Undiluted	2	1/10	200

C, concentration; IDT, intradermal test; INN, international nonproprietary name. Reproduced with permission [12].

Other considerations

Systemic reaction might occur during skin testing and IDT carries a higher risk than prick test for inducing an anaphylactic reaction [18]. The prevalence of anaphylaxis induced by skin testing has been estimated to be lower than 0.1 and 0.3% for antibiotics and NMBA, respectively [19,20].

Skin tests should therefore be performed by trained physicians in a setting with adequate resuscitative equipment. Pregnancy, young age and treatment with angiotensin-converting enzyme inhibitors or β -blockers agents are not contraindications for skin testing [12]. In contrast, others recommend discontinuing intake of β -blocker as these drugs may interfere with the treatment of a possible systemic reaction elicited by skin testing [18]. Nevertheless, the appreciation of the balance between risk (occurrence of an anaphylactic reaction following skin testing, which remains very low) and benefit (protective myocardial effect of β -blockers in ischaemic cardiomyopathy for example) acts in favour of the continuation of the β -blocker treatment [21[•]]. There are some limitations for skin testing: the pain of IDTs may limit their use in young children [18]; H_1 -antagonist receptors or vasoconstrictor drugs (ephedrine, neuroleptics, etc.), both modifying the skin reactivity, should be discontinued at least 5 days before skin testing [18]; dialysis as high tobacco consumption decreases the skin reactivity due to vasoconstriction; in contrast, the skin reactivity may be increased in case of dermatographism or chronic urticaria.

Finally, a consultation performed by a team including two physicians with expertise in anaesthesia and in allergy would be highly desirable in order to optimize the proper character of the diagnosis. Additionally, patients must be informed of the investigations and should possess a detailed study to provide it before eventual future anaesthesia.

Drugs and substances involved

NMBAs, latex and antibiotics are the molecules found responsible for anaphylaxis during the perioperative period with the highest frequencies.

Neuromuscular blocking agents: NMBA are the most common cause of anaphylaxis during anaesthesia at a range of 50–70%. All NMBA have been reported to cause anaphylaxis [6[•],10[•]]. The sensitivity of skin tests for NMBA in patients having experienced an anaphylactic reaction with an NMBA is superior than 95% and their reproductibility is excellent [20]. The estimated prevalence of cross-reactivity among NMBA is about 65% by skin tests [6[•]]. When the prick test and/or the IDT with an NMBA is positive, investigation for cross-reactivity with the other commercialized NMBA should be per-

formed by prick tests followed by IDTs. The maximal concentration recommended should not be exceeded (Table 2) [6[•],12,13[•]]. An NMBA negative by IDT might be proposed for a further re-introduction. Nevertheless, this recommendation does not guarantee absolute prevention from further adverse reaction.

Specificity of skin tests with NMBA is still a matter of discussion. Some authors [22,23] called into doubt whether skin tests can be applied to diagnose allergy from NMBA. These studies were performed in control patients keeping in mind the facts that they only refer to the histamine release properties of NMBA in control patients [24[•]]; the predictive value of skin tests performed in control patients remains unknown. In contrast, when skin tests are performed in patients having presented a perioperative immediate reaction, skin tests allow to identify the mechanism of the reaction as the culprit drug and therefore to ascertain a diagnosis; and to suggest an alternative NMBA negative by skin testing. Nevertheless, even if the determination of the maximal nonreactive concentration for each drug seems necessary in control patients to determine the maximal concentrations to use for the diagnosis of anaphylaxis [24[•]], skin tests performed either in control or anaphylactic patients cannot be compared.

Latex: In Europe, investigation of latex is performed by prick tests using commercial extracts which are not available in the United States [19]. The sensitivity of skin tests with latex is excellent.

Antibiotics: Penicillins and cephalosporins induce around 70% of perioperative anaphylactic reactions elicited by antibiotics [6[•]]. Skin testing should include amoxicillin and ampicillin. Different cephalosporins can also be used. Skin tests begin with prick tests followed by IDTs in case of negativity. The maximum concentrations have been proposed by the ENDA (European Network for Drug Allergy) interest group on drug hypersensitivity as follows: amoxicillin 20–25 mg/ml, ampicillin 20–25 mg/ml and for most cephalosporins 1–2 mg/ml [25]. In patients reporting severe reactions, prick tests should begin with a 1000-fold dilution which are gradually increased until the positive skin response or until reaching the maximum concentration. The specificity of skin testing with β -lactams is between 97 and 99%, whereas the sensitivity is around 50% [25]. The cross-reactivity between penicillins and cephalosporins appears to be low. In-vitro assays to quantify specific IgEs for several penicillin determinants are less sensitive than skin tests [6[•]]. Diagnosis of IgE-mediated reactions to non β -lactams is limited by a lack of knowledge of the relevant allergenic determinants. IgE-mediated reaction with vancomycin remains rare, but, if necessary, IDT with vancomycin should be performed below a concentration of 10 μ g/ml [6[•]]. Skin

tests with quinolones may be difficult to interpret due to histamine release. Other in-vitro cellular tests as cellular allergen stimulation test or flow cytometric basophil activation test have been proposed for the diagnosis of anaphylaxis to β -lactams. These techniques need to be validated.

Colloids: The overall frequency of anaphylaxis with colloids was estimated to be at 0.033–0.22% [9,26]. Skin tests begin with prick tests (1/10 dilution) followed by IDTs in case of negativity [12].

Aprotinin: The frequency of anaphylactic reactions with aprotinin is estimated at 0.5–5.8% [19,26]. Skin tests begin with prick tests (1/10 dilution or pure solution) followed by IDTs (from 1/1000 to 1/10 dilution) in case of negativity [12].

Dyes: The incidence of allergic reactions to isosulfan blue ranges from 1 to 2% [19]. Patent blue was involved in less than 1% of perioperative anaphylactic reactions [10^{*}]. Only one documented case of anaphylaxis due to methylene blue dye, structurally less related to isosulfan/patent blue, has been reported [27]. Dyes may be skin tested by prick tests followed by IDTs [27,28].

Opioids: Anaphylactic reactions to opioids are very rare. The sensitivity of IDT with morphine is good, whereas specificity is not because morphine induces histamine release. False positive skin tests (IDTs) are described when insufficiently diluted morphine is tested (1/1000 dilution is recommended and should not be exceeded). Phenylpiperidines (alfentanil, fentanyl, remifentanyl and sufentanyl) may be skin tested undiluted by prick tests followed by IDTs if negative (1/10 dilution should not be exceeded) (Table 2) [12].

Local anaesthetics: Anaphylactic reactions to local anaesthetics appear very rare when compared to their wide use. There is no cross-reactivity between ester and amid groups. Allergic reactions to the preservatives (methylparaben, paraben) of local anaesthetics solutions remain very rare. Local anaesthetics may be skin tested according to Table 2 [12].

Hypnotics: Thiopental was involved in less than 1% of allergic reactions in France [7]. A few cases have been reported with propofol representing less than 2.5% of anaphylactic reactions [7]. Anaphylactic reactions to etomidate and ketamine remain extremely rare. Hypnotics may be skin tested according to Table 2 [12].

Other drugs: Protamin, antiseptics (chlorhexidine, povidone iodine), contrast agents may also induce anaphylactic reactions. Skin testing may be performed to prove the diagnosis [10^{*},29].

Challenge tests

Challenge tests are limited to local anaesthetics and latex in case of negative skin tests. The tests are considered negative if no adverse reaction occurs within 30 min after injecting subcutaneously the local anaesthetic or wearing a latex glove [12,19].

Conclusion

Perioperative anaphylaxis is a potential life-threatening clinical condition which remains underestimated. NMBAs, latex and antibiotics are the most common drugs involved, but other drugs used for the anaesthesia or for the surgical procedure might be involved. An allergological assessment including biochemical tests and skin tests is required to prove the immune mechanism, to identify the culprit drug/substance and the cross-reactive molecules, especially for neuromuscular blocking agents, and to avoid it definitely in order to prevent further reactions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 421).

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