

DIAGNOSIS OF PERIOPERATIVE ANAPHYLAXIS

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SUMMARY

Every agent used during the perioperative period may be involved and have the potential to trigger both allergic, IgE and non-IgE reaction as well as non-specific (non-allergic) reactions. In many cases, an allergic mechanism cannot be ruled out and systematic investigations should be tested of all drugs and agents the patient was exposed to prior to the reaction. The complexity of agents used for anaesthesia and surgery present challenges when attempting to identify the culprit drugs and select proper testing to better recognition of trigger. The diagnosis of preoperative anaphylactic or anaphylactoid reaction is clinical and based upon the presence of characteristic symptom and signs that begin suddenly and developed rapidly in most cases. Elevations of mast cell mediators such as tryptase and histamine in the blood can help to distinguish anaphylaxis from other disorders that present with similar clinical picture. The secondary investigations of adverse perioperative drug reactions are highly specialised and include skin testing, in vitro testing and in some cases challenge tests. Any suspected reaction during anaesthesia must be extensively investigated and these diagnostic tests should be done in specialised centres. The cooperation between anaesthesiologists and allergists is necessary to provide the necessary diagnostic tests to identify the responsible drug, to carry out prevention and to provide recommendations for future anesthetic procedures.

Key words: anaphylaxis - perioperative - anaesthesia - anaphylactoid reactions - diagnostic tests

Abbreviations: BAT - basophil activation test; CAST - Cellular antigen stimulation test; Ig - Immunoglobulin;
 LHRT - leukocyte histamine release test; LT - leukotriene; NA - Not applicable or no concentration recommended;
 NSAID - Non-steroidal anti-inflammatory drug; NMBA - neuromuscular blocking agent; sIgE - Specific immunoglobulin E

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INTRODUCTION

During anaesthesia and pre and post anaesthesia period the anaesthesiologist routinely administers multiple agents, such as neuromuscular blocking agents (NMBAs) or other anaesthetic drugs, antibiotics, blood products etc. Majority of these have the potential to produce severe or life threatening hypersensitive reactions. Adverse, hypersensitive reaction during anaesthesia can be divided into two major types; allergic which can be IgE-mediated and non-IgE mediated drug allergy and drug intolerance and so-called pseudo-allergic or anaphylactoid reactions (Ebo et al. 2007, Johansson et al. 2004). Initially, the term anaphylaxis was used only for immunoglobulin E (IgE)-mediated reactions, whereas the term anaphylactoid was used for a reaction occurring via non-IgE-dependent mechanism. However, anaesthesiologists usually have little understanding of which drug is actually causing reaction when several drugs are simultaneously administered. Therefore, a new definition has been proposed by European Academy for Allergy and Clinical Immunology whereby all reactions are described as anaphylaxis and subdivided into allergic (IgE or IgG

mediated) or nonallergic anaphylaxis only after diagnostic investigations (Volcheck & Mertes 2014). Any suspected allergic or pseudoallergic reaction during anaesthesia must be extensively investigated using combined preoperative and postoperative testing. It is important to confirm the nature of the reaction, to identify the responsible trigger, to detect possible cross-reactivity and to propose recommendations for future anesthetic procedures (Norred 2012, Panjo et al. 2011). The diagnostic of suspected perioperative hypersensitive reactions involves a clinical history, review of records of the event, in vitro diagnostic tests obtained at the time of reaction or after, skin testing (skin prick or intradermal tests) and in some cases challenge tests.

The complexity of agents used for anaesthesia present challenges when trying to identify the trigger, but critical interpretation of clinical picture and proper testing leads to better recognition of culprit agents (Kroigaard et al. 2007). Whenever possible, confirmation of the suspected agent should be based on immunological assessment using more than one test. However, none of the available diagnostic tests for detection of perioperative drug hypersensitivity demonstrates absolute accuracy. False-

positive test results may to cause an unnecessary avoidance of a drug, while false-negative or equivocal results can be very dangerous and severely compromise correct secondary prevention (Kannan & Bernstein 2015).

PATIENT'S MEDICAL HISTORY AND MEDICAL RECORD

An initial step in analyzing a patient with suspected perioperative drug hypersensitivity is verification that the reaction was clinically consistent with anaphylaxis or anaphylactoid reaction with cutaneous, respiratory or cardiovascular signs and symptoms, as well as signs and symptoms of involvement of other organ systems. Actually, it is even more difficult in sedated or anesthetized patients recognition symptoms or signs of anaphylaxis (Brockow 2014). A review of medical and drug application records is essential to determine temporal relationships between the application of various agents and the onset of signs and symptoms. Operative notes may be helpful for identifying potential exposures to latex (eg, symptoms that began shortly after an internal organ was extensively manipulated and handled), as well.

The diagnostic strategy in the immediate as well as secondary investigation is based on a detailed history including concurrent morbidity, risk factors eg. atopy, asthma, food allergy, drug allergy and any known allergy previous anesthetic history and surgical procedures. However, questioning the patient about prior anesthesia may be helpful in identifying previous exposures as well as agents that were tolerated in the past (Mertes et al. 2010). Patients usually cannot provide much information about reactions that occurred during anesthesia. Therefore it is essential to attach a medical record with a detailed list of medicines and procedures applied during anesthesia, with the description of the symptoms and signs and the time of drug administration and the onset of symptoms, before referring the patient to an allergist.

IMMEDIATE DIAGNOSTIC TESTS IN PATIENTS WITH SUSPECTED PERIOPERATIVE ANAPHYLAXIS

The immediate diagnosis of anaphylaxis during the acute occurrence is based on the clinical picture and a history of a recent exposure to a causer agent (Ebo et al. 2007). It still does not available laboratory tests in an emergency department or in clinical laboratory to confirm a diagnosis of anaphylaxis in real time. Laboratory test obtained during or shortly after the acute event, help to support the clinical diagnosis of anaphylaxis or can help in differential diagnosis of anaphylaxis e.g. such as severe asthma or myocardial infarction. In addition, these tests may provide evidence for anaphylaxis as a cause of death. Available tests for the detection of the

following mast cell and basophiles mediators are available commercially; tryptase (serum/plasma), histamine (plasma), the histamine metabolite, N-methylhistamine (urine), the leukotriene, LTC₄ metabolite and LTE₄ (urine). In clinical practice, the most commonly used test for the measurement of serum/plasma tryptase (Laroche et al. 2014, Borer-Reinhold et al. 2011). Assays of other mast cell and basophil mediators, such as serum and urinary histamine, histamine metabolites, and leukotrienes, are of limited clinical value (Borer-Reinhold et al. 2011).

SERUM TRYPTASE

During an immunological reaction, basophiles and mast cells are activated, then degranulate and release mediators into the extracellular fluid compartment. These mediators can be measured in the patient's serum or plasma and have proved to be useful for the diagnosis of anaphylaxis or anaphylactoid reaction during anesthesia. Release of tryptase (alfa and beta) occur transiently following significant mast cell/basophiles activation. Elevations of mast cell/basophiles mediators in the blood can help to distinguish anaphylaxis from other disorders that present similarly, although normal tryptase levels do not exclude anaphylaxis (Kannan & Bernstein 2015).

Serum tryptase >11.4 ng/mL is considered elevated. However, a patient may have a much lower tryptase value at baseline, in which case an increase in serum total tryptase of 20 percent, or more than 2 ng/mL is accepted as marker of mast cell activation, even if the maximum increase is within the normal range. In most cases the patient's baseline serum tryptase is not known, therefore it is recommended to repeat the measurement of serum tryptase several days after the reaction. Tryptase concentration reach diagnostic levels within 30 minutes of the onset of a reaction, and as enzyme half-life is 2 hours, early collection of serum for testing is necessary. Although serum tryptase has a half-life of approximately two hours, elevated levels can be found longer following massive mediator release. It is recommended to collect blood for serum tryptase as soon as possible after the onset of symptoms in a red top tube, and a minimum of 1 mL of blood. Tryptase is stable in frozen serum for up to one year (Guyer et al. 2015, Veien et al. 2000).

On the other side tryptase levels may not be elevated even when a reaction is confirmed as anaphylactic or IgE mediated or in the absence of hypotension. An elevated level of serum tryptase indicates that mast cell/basophiles degranulation occurred, although it does not provide information about the mechanism of mast cell/basophiles activation (e.g., IgE-mediated or non-IgE mediated) or the culprit trigger. Tryptase was elevated in 68% of IgE-mediated reactions and 4% of non-IgE-mediated reactions in the largest French study

(Mertes et al. 2011 a). According to publication, the sensitivity of tryptase measurement for the diagnosis of anaphylaxis was estimated at 64%, its specificity at 89.3%, positive predictive value at 92.6% and negative predictive value at 54.3% (Laroche et al. 2014, Guyer et al. 2015, Veien et al. 2000). If serum tryptase is elevated, a repeat measurement should be performed when the patient is completely asymptomatic to assure that levels are not persistently elevated. Patients with persistent elevations above 20 ng/mL should be evaluated for the rare disorders, such as systemic mastocytosis. If the tryptase is above 11 ng/mL but less than 20 ng/mL, the individual may be at risk of anaphylaxis due to a monoclonal mast cell disorder or idiopathic mast cell activation syndrome (Kannan & Bernstein 2015, Laroche et al. 2014, Bridgman et al. 2013).

Serum that was collected at the time of the reaction for other reasons can sometimes be retrieved at a later time and assayed. Levels of tryptase can increase dramatically after death due to nonspecific mediator release during cell death. For post-mortem, blood should be collected from the femoral artery or vein and not from the heart (Laroche et al. 2014, Guyer et al. 2015, Vitte & Bongrand 2013).

SERUM HISTAMINE ASSAYS

Histamine as well as tryptase is a mediator released after activation and degranulation of circulated basophils. Histamine serum level is maximal almost immediately after onset of reaction and it quickly falls, with a half-life of about 20 min. Therefore, circulating concentration of histamine should be assayed within the first 30 minutes of the onset of reaction. In mild cases of anaphylaxis, only early serum concentration may be increased (Laroche et al. 2014). Increased levels of circulating histamine confirm basophil cell degranulation which can result from IgE-mediated activation of basophils. Histamine assays should be avoided during pregnancy and in patients receiving high doses of heparin because of accelerated histamine degradation due a high rate of false negativity. The sensitivity of histamina assays for the diagnosis of anaphylaxis was estimated at 75%, its specificity at 51%, the positive predictive value at 75% and the negative predictive value at 51%. Urinary methylhistamine assays are no longer recommended because of their low sensitivity in comparison with tryptase and serum histamine assays (Laroche et al. 2014, Veien et al. 2000).

SECONDARY INVESTIGATIONS OF ADVERSE PERIOPERATIVE DRUG REACTIONS

While the early tests are essentially to distinguish whether or not the adverse perioperative drug reactions are immunologically determined, secondary diagnostic

tests attempt to identify the responsible triggers. There are three main reasons of the secondary investigations of adverse perioperative drug reactions:

- To collect evidence to confirm or exclude that the adverse perioperative events was anaphylaxis.
- Identification of the responsible trigger so that the culprit agent can be avoided in the future.
- Identification of alternative drugs to which the patient has no evidence of hypersensitivity.

Secondary investigations include *in vitro* tests such as quantification of specific IgE and basophil activation tests (BAT) and *in vivo* tests such as skin tests and challenge tests (Fisher 2007, Mayorga et al. 2016, Laguna et al. 2018).

SERUM SPECIFIC IgE ASSEY

In vitro tests are available to detect the presence of serum specific IgE antibodies. In the diagnosis of allergy to drugs used perioperatively determination of drug specific IgE antibodies has been limited. There are commercially available tests for specific IgE to perioperative agents with varying sensitivity and specificity. Many centres use the ImmunoCAP system (Thermo-fisher, Uppsala, Sweden), and the specific IgE assay for chlorhexidine has been shown to have very high sensitivity and specificity (Opstrup et al. 2014). Specific IgE for latex and penicillins also show acceptable sensitivity and specificity, but for most of the other agents, validity is uncertain. Specific IgE can be measured at the time of the allergic reaction and has been shown to be elevated at this time for several allergens such as chlorhexidine, ethylene oxide and NMBA (Karila et al. 2005, Garvey et al. 2007, Opstrup et al. 2010), and during the secondary investigation, as well. Specific IgE levels will decrease over time on lack of exposure and may fall below the detection limit of 0.35 kUA/l, and therefore, a negative result cannot be used to rule out allergy. On re-exposure, specific IgE levels may increase again with or without a clinical relevant reaction (Karila et al. 2005). Serum specific IgE assays can alternatively be performed at the time of the reaction, or at the time of delayed skin test investigation. The delayed or secondary search for specific IgE in serum is based mainly on quaternary ammonium ions (reflecting IgE to NMBA), latex, thiopental, chlorhexidine, and occasionally β -lactams, according to the drugs administered to the patient (Guttormsen et al. 2007). *In vitro* assays to quantify specific IgEs for several beta-lactam antibiotic determinants are available but are generally considered less sensitive than skin tests (Ebo et al. 2007). Actually, in perioperative diagnosis of anaphylaxis indications for specific IgE assays to NMBA, thiopental and latex have been recommended (Guttormsen et al. 2007). These tests are usually performed several weeks (4-6 weeks) after the reaction (Guttormsen et al. 2007, Hemery et al. 2005).

LEUKOCYTE HISTAMINE RELEASE TESTS AND CELLULAR ALLERGEN STIMULATION TEST

In the clinical diagnostic practice, there are two main tests for detection of mediators after the allergen stimulation; leukocyte histamine release tests (LHR) and cellular allergen stimulation test (CAST) or sulphido-leukotriene release tests. Mata et al. have evaluated the LHR tests for the diagnosis of allergy to muscle relaxant drugs (Mata et al. 1992). Leukocyte histamine release tests were positive in 65 % of the allergic patients. The concordance between LHR test and sIgE (RIA method) was 64 % (Gueant et al. 1992). Diagnostic application in routine clinical practice despite a very good specificity, but insufficient sensitivity is very limited (Mertes et al. 2005). They could be useful when cross-reactivity among muscle relaxants is investigated with a view to future anesthesia in sensitized patients.

Similarly, detection of released LTC₄ measured by an ELISA by assay in after the cellular antigen stimulation (CAST-ELISA) has been published (Assem 1993) however, these assays cannot be recommended for routine clinical use at the present time (Mertes et al. 2005).

BASOPHIL ACTIVATION TEST (BAT)

Stimulation of peripheral blood basophils with specific antigen/allergen results with basophil activation and/or degranulation and release of various proinflammatory mediators from granules. Secreted mediators can be detected and quantifiable measured by different *in vitro* tests. One of the most commonly used test is the one that relies on the detection of changes in expression of basophil's cell membrane surface markers. Various combinations of the antibodies for basophils identification and detection of activation and/or degranulation are present nowadays on the market. Antibodies are labelled with fluorochromes and test samples measured on flow cytometer. The most commonly used combinations are shown in Table 1.

Table 1. Basophil identification and activation/degranulation markers

Identification	Activation / Degranulation
CCR3	CD63
IgE	CD203c
CD203c	Intracellular:
CD123 ⁺ HLA-DR ⁻	P38 MAPK
	STAT5

BAT is real functional test widely used in clinical diagnosis of various classical IgE-mediated allergies like inhalational allergies, food allergies, latex allergy, hymenoptera venom allergy and drug allergies (Abuaf et al. 1999). It represents a unique tool in the diagnosis

of IgE-independent hypersensitivity reactions as well as for the diagnosis of IgE-mediated anaphylaxis, specifically when a specific IgE assay is unavailable. Although differentiation in terms which activation pathway is involved, the IgE-dependent one or the IgE-independent, superior sensitivity and specificity of BAT has been described for many allergens when compared to other tests (Ebo et al. 2008, Monneret et al. 2000). However, still some controversies and issues remained. There is still no firm consensus about some technical aspects like: use of whole blood or isolated basophils, use of IL-3 as priming agent in stimulation buffer, dosages of allergens, appropriate negative and positive controls, controls positive and negative, best combination of identification and activation/degranulation markers and appropriate diagnostic threshold for different allergens (Ebo et al. 2008, Mayorga et al. 2016).

When BAT is used for drug allergy testing, usually combined approaches are applied when results are interpreted. Detection of positivity for CD63 is combined with calculation of Stimulation index (SI), which is ratio between percent of CD63⁺ basophils in allergen stimulated sample and percent of CD63⁺ basophils in unstimulated sample (negative control). For the drug allergens, results are considered positive if more than 5% of CD63⁺ basophils are detected and SI is ≥ 2 (Figure 1). Once all the aspects of the BAT will be fully validated and standardized, there is no doubt that BAT will represent a powerful diagnostic tool for NMBA anaphylaxis, as well as for cross sensitization studies. (Eberline et al. 2017, Mayorga et al. 2016)

SKIN PRICK-PUNCTURE AND INTRADERMAL TEST

The identification of agents causing IgE-mediated perioperative anaphylaxis include skin testing. Skin prick-puncture and intradermal test may be considered if the suspected agent is known to cause IgE-mediated reactions (Lafuente et al. 2013, Leynadier et al. 1987). Skin testing has no utility in the evaluation of anaphylactoid reactions, but generally a patient with suspected adverse perioperative reaction should be tested with each of the medications that were administered prior to or during the adverse reaction, placing priority on those agents most likely to cause anaphylaxis (Pepys et al. 1994, Brockow et al. 2013). Some agents capable of causing perioperative anaphylaxis and proposed mechanisms are shown in Table 2 (Ledford et al. 2018). For those medication that have been implicated in causing perioperative anaphylaxis through multiple mechanisms, such as neuromuscular-blocking agents (NMBA) recommended to perform skin testing for one or two potential alternative drugs. In the most cases, skin testing is more sensitive than *in vitro* testing, although the positive and negative predictive values of skin testing for most drugs is unknown (Brockow et al. 2013, Mertes et al. 2010).

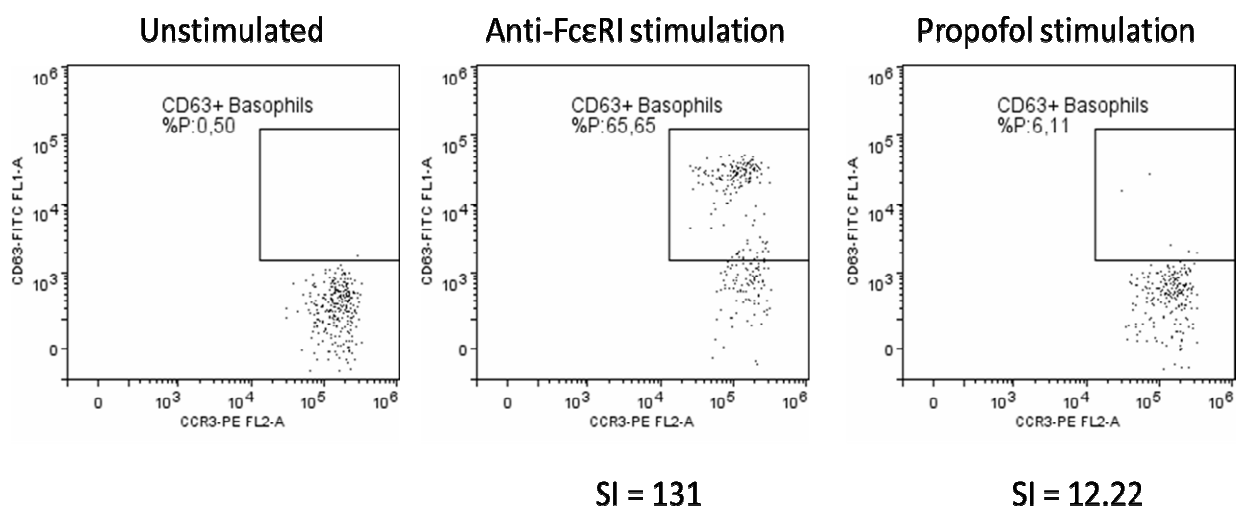


Figure 1. BAT results represented as % positive for CD63 and calculated SI

Table 2. Perioperative agents capable of causing perioperative anaphylaxis and proposed mechanisms (Ledford et al. 2018)

Agents	Immunologic reactions		Nonimmunologic
	IgE-mediated	Non-IgE-mediated	
Neuromuscular-blocking agents	+	-	+
Latex	+	-	-
Antibiotics	+	+/-	+
	(eg, beta-lactams)		(eg, vancomycin)
Hypnotic induction agents:			
Barbiturates	+	+	+
Nonbarbiturates	+/-	+	+
Opioids	+/-	-	+
Colloids and plasma expanders	+	+	+
Chlorhexidine	+	+/-	-

+/-: agent may cause anaphylaxis by this mechanism

The groups of agents that have most often been implicated in IgE-mediated perioperative anaphylaxis in which skin tests should be performed include:

- Neuromuscular-blocking agents (NMBAs);
- Certain antibiotics (particularly beta-lactam antibiotics, such as penicillin or cephalosporins);
- Latex (approved in vitro testing and skin testing in Europe);
- Vital dyes (isosulfan blue);
- Barbiturate induction agents (Chacko & Ledford 2007).

Skin testing, prick and intradermal to identify drug allergy should be performed by allergologist trained in the safe performance and accurate interpretation. Skin testing is considered safe for most patients, although it is not without risk. Prick testing is safer than intradermal testing and is preferred for the initial testing. If prick testing is negative, then intradermal testing can be performed. Intradermal testing is more sensitive than prick testing, but less specific. The maximal concentration used for intradermal testing is 10- to 1000-fold more dilute than that used for prick testing. However, these concentrations are often determined empirically (Brockow et al. 2013, Mertes et al. 2010, Chacko & Ledford 2007). If the con-

centration is too high, testing can induce either an irritant, nonspecific response or anaphylaxis. The concentration(s) chosen are dependent upon prior experience, expected risk of anaphylaxis or published case series, and rarely on controlled trials. Table 3 shows the most common perioperative agents and non-irritating concentrations for prick and intradermal testing (Mertes et al. 2010).

It is important to point out some practical advice regarding skin testing in suspected perioperative hypersensitivity reactions:

- If there is no recommended testing concentration available in the literature, it is recommended to start of prick testing with a 1:100 to 1:100,000 dilution of the concentration associated with the original reaction.
- Generally, the initial test concentration is based upon the severity of the reaction. A more dilute concentration can be used for the start of prick testing if the patient's reaction was severe.
- Repeat testing is performed with 10-fold increases in concentration until a positive prick test result or the clinically utilized concentration is reached.
- If all prick tests are negative, then intradermal testing is performed starting at 1:100 to 1:1000 of the maximum prick concentration (Brockow et al. 2013).

Table 3. The most common perioperative agents and non-irritating concentrations for prick and intradermal testing

Available Agents	Concentracion (mg/mL)	SPT		IDT	
		Dilution	C (mg/mL)	Dilution	C (mg/mL)
NMBAs					
Atracurium	10	1/10	1	1/1000	10
Cisatracurium	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	1/200	50
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Hypnotics					
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
Ketamine	100	1/10	10	1/100	1000
Opioids					
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Morphine	10	1/10	1	1/1000	10
Remifentanil	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Local anesthetics					
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1000
Mapivacaine	10	Undiluted	10	1/10	1000
Ropivacaine	2	Undiluted	2	1/10	200
Antibiotics					
PPL		Undiluted	0.035	Undiluted	35
MDM (penicillin)		Undiluted	1	Undiluted	1000
Penicillin G		Undiluted	20-25 x 10 ³	Undiluted	20-25 x 10 ³
AX, AMP		Undiluted	20-25	Undiluted	20-25 x 10 ³
Other penicillins					
Cephalosporins		Undiluted	1-2	Undiluted	1-2 x 10 ³
Vancomycin	500			1/5 x 10 ⁶	0.1
Gentamicin	40	Undiluted		1/10 ²	400
Miscellaneous					
Chlorhexidine	0.5	Undiluted	0.5	1/10	50
Patent blue	25	Undiluted	25	1/10	2500
Methylene blue	10	Undiluted		10	1/100

- Serial tests with 10-fold progressive increases in concentration are subsequently performed.
- An appropriate positive and negative controls are always necessary.
- Skin tests are interpreted after 15 to 20 min.
- A prick test is considered positive when the diameter of the wheal is at least equal to half of that produced by the positive control test and at least 3 mm greater than the negative control. Intradermal tests are considered positive when the diameter of the wheal is twice or more the diameter of the injection wheal.
- A false-positive irritant reaction may occur with both prick and intradermal testing, the results should be carefully interpreted or tested with additional dilutions
- testing should be carried out by a professional experienced allergologist in performing and interpreting tests with perioperative agents
- It is recommended that emergency medication (epinephrine) and equipment be available for treatment of the rare, but potentially life-threatening anaphylaxis that can appear during the testing
- Routine skin testing with perioperative agents is not recommended
- Skin testing is conducted at least 4-6 weeks after the occurrence of the suspected perioperative allergic reaction (Mayorga et al. 2016, Brockow et al. 2013, Mertes et al. 2010, Chacko & Ledford 2007, Trautmann et al. 2016).

CHALLENGE TEST IN INVESTIGATION OF ALLERGY TO PERIOPERATIVE AGENTS

Indication for the challenge or provocation tests in investigation of allergy to perioperative agents are limited. Challenge test is rarely considered in the investigation of perioperative allergy due to the pharmacological effect of most drugs and has only been recommended for, e.g. antibiotics, local anaesthetics and latex, when skin tests were negative or not possible to performed (Mertes et al. 2011 b). However, provocation is the gold standard in drug allergy and is helpful in confirming or disproving inconclusive skin test results (Mayorga et al. 2016).

They are restricted to local anesthetics, β -lactams and latex (Bousquet et al. 2008, Demoly et al. 2009). They should only be performed in case of negative skin tests. Local anesthetics can be tested by subcutaneously injecting 0.5 to 2 mL of undiluted anesthetic solution (without epinephrine). The test is considered negative if no adverse reaction occurs within 30 minutes after injection (Fisher & Bowey 1997). Oral provocation tests are useful for the diagnosis of beta-lactam hypersensitivity (Bousquet et al. 2008, Demoly et al. 2009). If the skin test to NMBA was negative and there is concern that a non-IgE mediated reaction to NMBA may have been suggestive then a challenge test would be the only definitive test of excluding this possibility. Certainly, the challenge test with NMBA is not feasible, because it would require inducing paralysis. In that case, in patients with clinically suspected reaction to NMBA with negative skin test, should be recommended to the patient an alternative agent to which the patient has been skin tested and found to be negative. Drug provocation test with other perioperative agents should be performed when there are no alternatives to performing the alternative anesthesia or alternative drugs, in the adequate centre by well-trained allergologist (Mayorga et al. 2016, Laguna et al. 2018). If there is no alternative drug with a negative skin test, then the suspect drug could be used again following premedication with antihistamine and possibly glucocorticoid (Mayorga et al. 2016, Laguna et al. 2018, Simons et al. 2011).

IMPORTANCE OF DIAGNOSTIC TESTS IN THE PREVENTION OF PERIOPERATIVE ANAPHYLAXIS

An important point in the prevention of future perioperative anaphylaxis is the identification of the possible trigger. In fact, prevention of future perioperative anaphylaxis require the identification of patients at risk, as well as taking into account all potential agents such as large number of drugs, diagnostic reagents, devices containing latex, antiseptics, and blood products which

are all routinely used during anesthesia. Sufficient knowledge of pathogenic mechanisms involved in systemic reactions to general anesthetics is essential to optimize prevention strategies. It is widely recognized that anaphylactic (IgE-mediated) events usually occur after repeated administration of sensitizing agents (Mayorga et al. 2016, Laguna et al. 2018, Ewan et al. 2010, Kannan & Bernstein 2015, Trautmann et al. 2016). These events are somewhat predictable in high-risk patients or in subjects who have had anaphylactic reactions previously. In the most cases, medical history and diagnostic tests are able to identify a culprit agent, however in that cases an alternative agent or procedure must be used or suggest. Avoidance of the allergens may demand a change in anesthetic plan like the choice of local anesthesia or nerve blocks or epidural anesthesia over general anesthesia. For patients who require repeat anesthesia, general precautionary measures include optimal preoperative control of asthma, slow administration of antibiotics and other high-risk agents, and avoidance (when possible) of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and drugs that cause direct histamine release from mast cells/basophils. After an evaluation is performed in which culprit drugs are identified, the patient should be educated about the specific agent that likely caused the reaction and informed about how best to avoid this and any potentially cross-reacting drugs. The results of the evaluation and advice about avoiding future reactions should be relayed to the patient's primary care health professional, anesthesiologist, and surgeon. The patient should consider obtaining a medical identification bracelet or similar device that lists the culprit drug(s) (Mayorga et al. 2016, Laguna et al. 2018, Kannan & Bernstein 2015, Trautmann et al. 2016).

IMMEDIATE TREATMENT OF ANAPHYLAXIS

With suspected anaphylaxis caused by the drug, stop administration of the drug (remove the trigger). It is important to recognize and apply the scheme ABCDE (Airway-Breathing- Circulation-Drugs-Exposure). Life-threatening complications must be adequately resolved. If cardiorespiratory arrest occurs immediately start reanimation following Advanced life-support (ALS) guidelines. Supplemental oxygen, facial masks at >10 liters/minute flow rate of 100% oxygen, should be administered until early endotracheal intubation if marked stridor or respiratory arrest is present (Mihaljević & Čačić 2016, Soar et al 2016). The first and most important treatment in anaphylaxis is epinephrine. It should be administered as soon as anaphylaxis is recognized to prevent the progression to life-threatening symptoms. Delayed epinephrine injection is associated with fatalities (Campbell & Kelso 2017).

Intramuscular application (IM) of adrenaline is the easiest and fastest. IM has several advantages:

- greater therapeutic safety;
- i.v. access is not required;
- it is easy to learn;
- the best place for application is the anterolateral side of the middle third of the thigh; with appropriate needle; giving adrenaline dose subcutaneous (SC) or inhaled is ineffective for their use.

Doses for IM application:

- there is not enough data to show us exactly the required dose; exhibit experience and practicality in the emergency situation;
- (volume at a dilution of 1:1000 are indicated in parentheses);
- 12 years old and for adults 500 mcg (0.5 ml) IM;
- 6-12 years old 300 mcg (0.3 ml) IM;
- 6 months - 6 years 150 mcg (0.15 ml) IM;
- < 6 months 150 mcg (0.15 ml) IM.

If the reaction on i.m. injection fails, repeat administration after 5 minutes.

Patients in whom was ineffective intramuscular application, may benefit from intravenously (IV) administration of the drug. When intravenous administration of adrenaline is used it is increased risk of side effects due to wrong dosage or wrong recognize anaphylaxis. IV administration of adrenaline should be left only for experienced medical staff (eg. Anesthesiologists, intensivists, specialists in emergency medicine). In patients with spontaneous held bloodstream, intravenously administered adrenaline can cause life-threatening hypertonia, tachycardia, arrhythmias and myocardial ischemia.

IV bolus in adults: Titrate adrenaline in the 50-microgram (mcg) boluses while therapy does show effect. If repeated bolus administration is necessary, it is recommended continuous administration of adrenaline infusion.

IV bolus in children: intramuscular application is recommended. IV administration of the drug should be administered in the presence of qualified staff (children's anesthesiologist, pediatrician, children's intensive care). There are no data on which to base a adequately dose- it should be titrated by the effect and expected dose of 1 mcg/kg should be effective (Mihaljević & Čačić 2016, Soar et al 2016, Mali 2012)

Patients must be closely monitored because of side effects listed above (ECG, blood pressure, oxygen saturation). Postoperative intensive care admission should be organized for monitoring because anaphylactic reaction can be prolonged up to 32 hours and biphasic reactions occur in up to 20% of cases without new exposure to trigger (Mali 2012).

Two large-bore IV catheters should be inserted for rapid administration of fluids and medications. Intraosseous access should be obtained if IV access is not readily obtainable. Optimisation of cardiovascular status by intravenous fluid resuscitation (Fluid challenge boluses for children 20 ml/kg and 500-1000 ml in adults until clinical effect occur) (Mali 2012). In addition to standard monitoring, invasive blood pressure monitoring allows better epinephrine titration and a central venous catheter facilitates administration of vasopressors and inotropes (Mali 2012).

SECOND LINE TREATMENT

After initial resuscitation antihistamines may help counter histamine-mediated vasodilatation and bronchoconstriction. Intravenous antihistamine may carry more risks than benefits, including the risk of hypotension with rapid injection and tissue injury if extravasated.

Corticosteroids may help prevent or shorten protracted reactions. Both drugs have slow onset of action and have not been proven to alter the clinical outcome (Mali 2012, Campbell & Kelso 2017).

CONCLUSIONS

Perioperative anaphylaxis can result from more than one mechanism, and it is important to understand which mechanisms are associated with each agent, as well as what type of testing is relevant for that mechanism. Identification of the offending perioperative agent is difficult, and patients are not always referred for post-operative testing. Diagnostic testing may confirm or exclude causative agent in some patients only. NMBA, latex and antibiotics are the most common causes of perioperative anaphylaxis, and prevention is the most important component to decrease the risk. Post-operative referral to an allergist for identification of the causative agents is important to prevent future incidents of perioperative anaphylaxis.

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Mirjana Turkalj & Damir Erceg: study design, manuscript preparation.

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References

1. Abuaf N, Rajoely B, Ghazouani E, et al. Validation of a flow cytometric assay detecting in vitro basophil activation for the diagnosis of muscle relaxant allergy. *J Allergy Clin Immunol* 1999; 104:411-418
2. Assem E. Leukotriene C4 release from blood cells in vitro in patients with anaphylactoid reactions to neuromuscular blockers. *Agents Actions* 1993; 38:C242-C244.
3. Borer-Reinhold M, Haerberli G, Bitzenhofer M, et al. An increase in serum tryptase even below 11.4 ng/mL may indicate a mast cell-mediated hypersensitivity reaction: a prospective study in Hymenoptera venom allergic patients. *Clin Exp Allergy* 2011; 41:1777
4. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 2008; 38:185-90
5. Bridgman DE, Clarke R, Sadleir PH, et al. Systemic mastocytosis presenting as intraoperative anaphylaxis with atypical features: a report of two cases. *Anaesth Intensive Care* 2013; 41:116
6. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; 68:702
7. Brockow K. Dilemmas of allergy diagnosis in perioperative anaphylaxis. *Allergy* 2014; 69:1265
8. Campbell & Kelso: *Anaphylaxis: Emergency treatment*, 2017
9. Chacko T, Ledford D: *Peri-anesthetic anaphylaxis*. *Immunol Allergy Clin North Am* 2007; 27:213
10. Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2009; 26:76
11. Eberline B, Wigand S, Lewald H, Kochs E, Ring J, Biedermann T, et al. Utility of basophil activation testing to assess perioperative anaphylactic reactions in real-world practice. *Immunity, Inflammation and Disease* 2017; 5:416-20
12. Ebo DG, Bridts CH, Hagendorens MM, Aerts NE, De Clerck LS, Stevens WJ. Basophil activation test by flow cytometry: Present and future applications in allergology. *Cytometry B Clin Cytom* 2008; 74B:201-210
13. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; 62:471-87
14. Ewan PW, Dugue P, Mirakian R, et al. BCACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy* 2010; 40:15-31
15. Fisher MM, Bowey CJ. Alleged allergy to local anaesthetics. *Anaesth Intensive Care* 1997; 25:611-4
16. Fisher MM. The preoperative detection of risk of anaphylaxis during anaesthesia. *Anaesth Intensive Care*. 2007; 35:899-902
17. Garvey LH, Krøigaard M, Poulsen LK, Skov PS, Mosbech H, Venemalm L, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; 120:409-15
18. Gueant JL, Masson C, Laxenaire MC. Biological tests for diagnosing the IgE-mediated allergy to anaesthetic drugs. In: Assem K, ed. *Monographs in Allergy*. Basel: Karger; 1992; 94-107
19. Guttormsen AB, Johansson SG, Oman H, Wilhelmsen V, Nopp A. No consumption of IgE antibody in serum during allergic drug anaphylaxis. *Allergy* 2007; 62:1326-30
20. Guyer AC, Saff RR, Conroy M, et al. Comprehensive allergy evaluation is useful in the subsequent care of patients with drug hypersensitivity reactions during anesthesia. *J Allergy Clin Immunol Pract* 2015; 3:94
21. Hemery ML, Arnoux B, Rongier M, Barbotte E, Bousquet J, Demoly P. Correlation between former and new assays of latex IgE-specific determination using the K82 and K82 recombinant allergens from the Pharmacia Diagnostics laboratory. *Allergy* 2005; 60:131-132
22. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113:832-6
23. Kannan JA, Bernstein JA. Perioperative anaphylaxis. *Immunol Allergy Clin N Am* 2015; 35:321-34
24. Karila C, Brunet-Langot D, Labbez F, Jacqmarcq O, Ponvert C, Paupe J, et al. Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. *Allergy* 2005; 60:828-34
25. Krøigaard 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
26. Lafuente A, Javaloyes G, Berroa F, et al. Early skin testing is effective for diagnosis of hypersensitivity reactions occurring during anesthesia. *Allergy*. 2013;68:820.
27. Laguna JJ, Archilla J, Dona I, Corominas M, Gastaminza G, Mayorga C, et al. Practical Guidelines for Perioperative Hypersensitivity Reactions. *J Investig Allergol Clin Immunol* 2018; 18 (in press)
28. Laroche D, Gomis P, Gallimidi E, et al. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014; 121:272
29. Ledford DK, Adkinson NF, Feldweg AM. Perioperative anaphylaxis: Evaluation and prevention of recurrent reactions. *UpToDate* 2018. <https://www.uptodate.com>
30. Leynadier F, Sansarricq M, Didier JM, Dry J. Prick tests in the diagnosis of anaphylaxis to general anaesthetics. *Br J Anaesth* 1987; 59:683
31. Mali S. Anaphylaxis during the perioperative period. *Anesth Essays Res* 2012; 6:124-133
32. Mata E, Gueant JL, Moneret-Vautrin DA, et al. Clinical evaluation of in vitro leukocyte histamine release in allergy to muscle relaxant drugs. *Allergy* 1992; 47:471-476
33. Mayorga C, Celik G, Rouzair P, Whitaker P, Bonadonna P, Rodrigues-Carnades J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/ EAACI Drug Allergy Interest Group position paper. *Allergy* 2016; 17:1103-134
34. 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
35. Mertes PM, Laxenaire MC, Lienhart A, et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2005; 15:91-101

36. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anaesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; 21:442-53
37. Mertes PM, Tajima K, Regnier-Kimmoun MA, et al. Perioperative anaphylaxis. *Med Clin North Am* 2010; 94:761
38. Mihaljević & Čačić: Kardiopulmonalna reanimacija, 2016; 190-196
39. Monneret G, Benoit Y, Gutowski M, Bienvenu J. Detection of basophil activation by flow cytométrie in patients with allergy to muscle-relaxant drugs. *Anesthesiology* 2000; 92:275-277
40. Norred CL. Anesthetic-induced anaphylaxis. *AANA* 2012; 80:129-40
41. Opstrup MS, Malling HJ, Krøigaard M, Mosbech H, Skov PS, Poulsen LK, et al. Standardized testing with chlorhexidine in perioperative allergy a large single centre evaluation. *Allergy* 2014; 69:1390-6
42. Opstrup MS, Mosbech H, Garvey LH. Allergic sensitization to ethylene oxide in patients with suspected allergic reactions during surgery and anesthesia. *J Investig Allergol Clin Immunol* 2010; 20:269-70
43. Panjo GB, Crisafulli J, Calminiti L, Marseglia GL, Cardinale F, Paravati F, Caffarelli C. Peri-operative allergy: Therapy. *Int J Immunopath Phar* 2011; 24:101-4
44. Pepys J, Pepys EO, Baldo BA, Whitwam JG. Anaphylactic/anaphylactoid reactions to anaesthetic and associated agents. Skin prick tests in aetiological diagnosis. *Anaesthesia* 1994; 49:470
45. Simons FER, Arduzzo LRF, Bilo MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organ J*. 2011; 4:13-37
46. Soar et al.: Emergency treatment of anaphylactic reactions: Guidelines for healthcare providers, resuscitation council (UK), 2016
47. Trautmann A, Seidl C, Stoevesandt J, Seitz CS. General anaesthesia-induced anaphylaxis: impact of allergy testing on subsequent anaesthesia. *Clin Exp Allergy*. 2016;46:125
48. Veien M, Szlam F, Holden JT, et al. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. *Anesthesiology* 2000; 92:1074
49. Vitte J, Bongrand P. Serum tryptase determination in patients with acute allergic reactions. *J Allergy Clin Immunol* 2013; 131:1714
50. Volcheck GW, Mertes PM, Local and General Anesthetics Immediate Hypersensitivity Reactions. *Immunol Allergy Clin North Am* 2014; 34:525-46

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