Anaphylactic reactions during anaesthesia and the perioperative period

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Abstract

Allergy and hypersensitivity occurring during anaesthesia remains a major cause of concern for anaesthesiologists. Drugs administered during surgery and various anaesthetic procedures can elicit two major groups of adverse reactions. The first group includes reactions that are usually dose-dependent and related to the pharmacological properties of a drug and/or its metabolites. The remaining reactions are mostly related to hypersensitivity and allergic responses. They do not depend on specific pharmacology and are usually not dose-dependent.

Anaphylaxis is among the most severe of immune-mediated reactions; it generally occurs following re-exposure to specific antigens and release of proinflammatory mediators. The commonest drugs responsible for intraoperative anaphylaxis are muscle relaxants, but latex also accounts for a significant number of incidents, and the frequency of intraoperative latex anaphylactic reactions is increasing. Multiple organ failure, beginning with bronchospasm and cardiovascular collapse, is typical of latex reactions. An increased serum tryptase concentration confirms the diagnosis of an anaphylactic reaction, and triggers can be identified by skin prick, intradermal injection, or serologic testing.

The elimination of triggers during subsequent medical episodes is essential to avoid major mortality and morbidity.

Key words: complications, anaphilaxis, muscle relaxants; complications, anaphilaxis, anaesthetics; complications, anaphilaxis, latex

Perioperative safety of patients is a major concern of anaesthetists. Anaphylactic reactions, the critical events that can occur during the perioperative period, are not exclusively related to anaesthetic procedures. They also strictly depend on meticulous qualification of patients for surgeries carried out by operators.

Drugs administered during the anaesthetic procedure and postoperative period belong to different pharmacological groups and are to ensure the best possible conditions for surgery and maximum safety of patients. Their adverse side effects are often dependent on immune responses. The diversity and number of the agents administered hinder precise determination of the drug eliciting the adverse drug reaction. According to the Danish data, the number of potential allergens the patient is exposed to during anaesthesia ranges from 7 to 9 [1, 2, 3].

The reactions accompanying anaesthesia suggestive of anaphylaxis belong to the most complex and unpredictable adverse drug reactions (ADRs) in the perioperative period. ADR is defined as a noxious, unintended response to standard doses of a given agent. During anaesthesia, when surgical interventions are carried out, patients are exposed to many substances, i.e. anaesthetics, antibiotics, blood preparations, heparin, polypeptides (aprotinin, latex and protamine sulphate), and fluids supplementing the circulating blood volume. The definition of an adverse drug event (ADE) is less precise, involving also the consequences of improper use or overdose of a particular drug [4, 5]. ADE is the reaction that can occur in any patient during and after treatment, which does not have to (albeit can) be triggered by the drug used.

There are only a few Polish reports concerning epidemiology, diagnosis and description of adverse reactions raising suspicion of anaphylaxis during the perioperative period. In general, their incidence is low and mortality rates are not precisely determined. The estimated number of anaesthesia-related deaths in Poland is 1.47/10 000 anaesthetic procedures [6]. The literature data regarding ana-
Phylactic reactions during anaesthesia differ according to a particular geographical region and range between 1/6000 and 1/20 000 of the total number of anaesthesias (regional and general) [7, 8]. In Great Britain, 361 such reactions were reported to the ADR notification centres between 1986 and 1993 [9, 10]. In France, 798 cases of ADRs were reported to such Notification Centres in the years 1993–1995 [11]. Unfortunately, no such centres were created in Poland (at least until the end of 2009). Moreover, a uniform system of notification and diagnosis of ADR is still lacking; the majority of mild reactions are undetected, ignored and undiagnosed.

In most cases, the symptoms of ADR develop within several minutes after the exposure to a triggering factor. The quicker and more rapid the onset, the higher the life threat is. The first manifestations occur in the skin involving the mast cell-rich areas (face, neck, anterior thorax) and quickly become generalized [12]. Occasionally, the first symptoms regard the cardiovascular or respiratory system, less commonly, the gastrointestinal system. Moreover, the symptoms can be invisible or unnoticeable as the anaesthetised patients are covered.

The studies published since 1980 describe 4500 cases of anaphylaxis during anaesthesia documented by allergological tests [12, 13]. The most common triggers of ADRs reported in literature include neuromuscular blocking agents (62%), latex (16.5%), intravenous anaesthetics (7.4%), prophylactic antibiotics (4.7%), colloids (3.6%), and opioids (1.9%) [8, 10, 12, 13, 14]. The majority of descriptions of anaphylaxis during anaesthesia concern case reports.

The multi-centre studies carried out in France by the Groupe d’Études des Réactions Anaphylactoides Perane-thésiques (GERAP) are of essential significance to elucidate the epidemiology of the phenomena in question [14].

The adverse reactions are likely to occur at any stage of anaesthesia; however, the majority of them are observed within the first minutes following the intravenous drug administration [15]. Thanks to comprehensive management of each patient who experienced the immediate drug-related reaction during anaesthesia, the trigger can be determined and instructions for future anaesthetic procedures established. The diagnosis is based on the documented clinical symptoms according to the anaesthetic protocol, specially designed questionnaires, which describe the chronology of events, and results of biological material and skin tests.

Anaesthetists should record the occurrence of ADR in the anaesthetic chart and provide the patient with the information card containing the description of that reaction. Each patient is referred to an allergologist, who should be provided with all suitable information by the attending anaesthetist. Further anaesthetic procedures should not be performed as they endanger the patient’s life.

**Classification of Immune-Mediated Drug Hypersensitivity Reactions**

The term “allergy” and attempts to define it date back to the beginning of the 20th century, although the diseases later defined as allergies were known much earlier [16, 17]. Anaphylaxis was first reported about one hundred years ago by Paul Jules Portier and Charles R. Richet, who described acute medusa venom-induced anaphylactic reaction in a dog [17, 18]. This paved the way for the concept of allergy, introduced by Clemens von Pirquet in 1906 to describe hypersensitivity of pre-sensitised organisms [19]; the term “anaphylaxis” started to mean acute life-threatening hypersensitivity reactions occurring in pre-sensitised animals and humans and were associated with specific immunity and effects of histamine [20].

Von Pirquet combined the Greek words *allos* (‘different’ or ‘changed’) and *ergos* (‘work’ or ‘action’). Since then the term allergy has not changed its meaning and allergologists have started to be interested in hypersensitivity reactions, leading to the development of disease symptoms. The diagnosis of allergy requires absolute certainty that the trigger was an allergen, i.e. the factor earlier recognised by the immune system as an antigen.

The major concern was associated with hypersensitivity reactions, whose symptoms were anaphylaxis-like yet did not result from earlier sensitization. In 1914, Emil von Behring termed such reactions as “anaphylactoid” ones [21].

The clinical pictures of adverse reactions are often diverse and depend on the type of immune reactions and the organs affected. If the mixed immunopathogenetic mechanism is involved, the reaction is difficult to classify according to the established division of hypersensitivity reactions in man. On the other hand, the characteristics and mechanisms of many allergic drug reactions correspond to the main categories described by Gell and Coombs in 1963: immediate hypersensitivity — type 1, cytotoxic reactions — type 2, immune complex-dependent reactions — type 3 and delayed cell-mediated hypersensitivity reaction — type 4 [22]. In this classification, anaphylaxis is defined as a group of signs and symptoms characteristic of immediate allergic reactions [17]. Once the role of IgE as a carrier of immediate allergic reactions was discovered, anaphylaxis started to be defined only as the group of dramatic symptoms of IgE-dependent allergy.

In 2003, the experts of the European Academy of Allergology and Clinical Immunology (EAACI) and World Allergy Organisation (WAO) suggested that anaphylaxis should be the overriding term describing all severe, life-threatening systemic and generalized reactions caused by allergic and non-allergic hypersensitivity [16, 20].

The term of allergic anaphylaxis should be used when the reaction is mediated by the IgE- or immune complex-dependent immunologically mediated mechanism. An-
Phylaxis conditioned by IgE can be termed as IgE-dependent allergic anaphylaxis. In contrast, for anaphylaxis resulting from any non-allergic cause, the term non-allergic reaction should be used. According to such definitions, the concept of anaphylaxis includes not only shock but also extremely severe isolated bronchospasm.

Adverse drug-related reactions (antibiotics, sulphonamides, muscle relaxants, anticonvulsants, hormones, etc.) occur in predisposed patients. The majority of anaesthetized individuals have never had any contact with anaesthetics. In this group of patients, non-allergic hypersensitivity reactions are mostly observed. The IgE-dependent allergic reaction can develop in the patient after the first contact with a drug, if the patient was earlier allergic to one of the drug components. This mechanism of hypersensitivity occurs after administration of neuromuscular blocking agents (NMBAs). An epitope recognized by IgE is the quaternary ammonium ion [23], which explains high incidences of cross-reactions to individual NMBAs. The immune system is involved in the pathogenesis of these reactions (immunologically mediated drug hypersensitivity reactions). When the reaction is induced through the non-immune pathway and the clinical picture resembles an allergic reaction, non-allergic hypersensitivity occurs, which includes intolerance-related, unpredictable reactions defined as pseudo-allergies. They can be induced by non-steroidal anti-inflammatory drugs (NSAIDs), radiological contrast agents, mannitol, local anaesthetics (LAs), dextran or NMBAs. Moreover, such reactions can be caused by various mixed mechanism. One of them is complement system activation, which leads to the formation of potent anaphylatoxins C3a and C5a, which can directly trigger degranulation of mast cells and basophils releasing the same strong mediators. Another mechanism — IgE and complement system-independent — involves the direct action of certain factors on mast cells, basophils, vascular endothelium [24]. Such factors stimulate the release of mediators.

ANAESTHETIC AGENTS POTENTIALLY RESPONSIBLE FOR TRIGGERING ADVERSE REACTIONS

The list of agents suspected of triggering the life-threatening reactions during anaesthesia is extremely long. The ranking of individual preparations and their groups markedly depend on the therapeutic standards used in individual countries.

NEUROMUSCULAR BLOCKING AGENTS

Allergies to NMBAs have been known since 1967, when Jarmus described the IgE-dependent reaction to suxamethonium [24]. In recent years, many novel NMBAs were introduced, which reduced the use of suxamethonium to facilitate intubation. The drug was the commonest trigger of anaphylactic reactions [25].

The incidence of anaphylactic reactions to NMBAs varies in different countries. According to French findings, NMBAs are responsible for 61.6% of hypersensitivity reactions in the population of 477 patients subjected to anaesthetic procedures. The commonest triggers of such reactions were found to be vecuronium (28.8%), atracurium (23.7%) and suxamethonium (23.5%) [26]. Despite its direct release of histamine, atracurium is responsible only for 0.2–5% of adverse reactions [12]. Anaphylaxis after pancuronium and vecuronium is observed most rarely. As far as rocuronium is concerned, once numerous adverse reactions to this agent were reported, the Norwegian Medical Centre decided to withdraw it from everyday practice, unless some specific indications are involved [27]. Anaphylactic reactions to rocuronium in Norway are estimated at 1/5000 anaesthetic procedures compared to 1/114 000 in other Scandinavian countries [28].

GENERAL ANAESTHETICS

The incidence of anaphylactic reactions to thiopentone is assessed as 1/30 000 [29]. The first such reactions were described during the World War II [23]. It was then suggested that the reactions in questions were induced by the release of histamine; when the role of IgE as a carrier of immediate allergic reactions has been established, the reaction after thiopentone is considered as the group of symptoms of IgE-dependent allergy [7].

Since the withdrawal of cremophor EL, a solvent of non-barbital agents, the number of anaphylactic reactions has decreased [30]. Propofol is a lipid emulsion containing soya oil, glycerol and lecithin. The risk of propofol-related anaphylactic reactions is low (1/60 000 cases) [26]. The mechanism of these reactions is most likely associated with the histamine release by mast cells.

The ketamine–related anaphylactic reactions are extremely rare [1] and the data concerning their mechanisms are scarce. It is suggested that direct effects of the anaesthetic on mast cells are involved.

The anaphylactic reactions after morphine, codeine, fentanyl, remifentanil and their derivatives are rare and their incidences are comparable [18]. The administration of the above drugs is associated with increased blood concentration of histamine [14]. In the French epidemiological studies carried out between 2000 and 2002, only seven cases of ARDs after opioids were found [31].

According to the available literature data, there were no intraoperative anaphylactic reactions to volatile anaesthetics.

LOCAL ANAESTHETICS

The allergic reactions to LAs are sporadic; their incidence is estimated at 1% of all immediate hypersensitivity reac-
ions to drugs administered during anaesthetic procedures [1]. The study encompassing 208 patients demonstrated 4 immediate and another 4 delayed hypersensitivity reactions [32]. The majority of pseudo-allergic reactions are vasomotor reactions, toxic reactions after unintended intravenous administration and symptoms caused by the addition of adrenalin to LAs solutions. Two groups of LAs are commonly used: p-aminobenzoic acid esters, rich sources of potential allergens and amide compounds, practically free of immunogenic properties [33]. The commonest reaction to LAs is the delayed response (type IV) in the form of contact dermatitis [32].

**ANTIBIOTICS**

The antibiotics widely used for perioperative prevention frequently cause hypersensitivity reactions. Only some proportion of these reactions is IgE-dependent or IgE-independent allergy. In cases with the documented immunological mechanism, the reactions are categorised as non-allergic hypersensitivity; their number is estimated at 2–8% [34]. The reactions induced by individual antibiotics are mostly observed after penicillins (0.004–0.015%) and cephalosporins (0.0001–0.1%) [1]. The risk of vancomycin-related reactions is comparable. Vancomycin can elicit “the red man syndrome” characterized by generalized erythema, pruritus, urticaria (usually affecting the face, neck and nape), and decreased arterial pressure [35]. The syndrome develops during fast intravenous administration of the drug and is caused by the release of non-specific mediators from mast cells and basophils. The second IgE-dependent type of reaction is exceptionally rare. Noteworthy, all types of antibiotics are potential causes of anaphylaxis [36].

**PROTAMINE SULPHATE**

In recent years, protamine sulphate-related reactions are increasingly common. Protamine sulphate is an antithromboplastin, inhibiting clotting and inactivating the effects of heparin [1]. The carriers of immediate hypersensitivity reactions are IgE and IgG antibodies [8]. In the study conducted amongst 243 patients anaesthetised for coronary artery bypass grafting, the adverse reactions were observed in 6 (2.4%) whereas arterial pressure alterations immediately after administration in 4 individuals (1.6%) [7].

**LATEX**

Allergy to latex is the second most serious cause of adverse reactions during anaesthesia. The typical reaction occurs 30–60 min after the onset of surgical procedure, and is rarely observed during induction of anaesthesia. The first case of latex allergy was described by Turjanmäki in 1984 [37]. In adults, severe reactions develop during intra-abdominal surgeries. In children operated on due to congenital defects (rachischisis) and urogenital defects, latex is the basic cause of anaphylaxis [38]. All children with rachischisis should be included in the high-risk latex allergy group immediately after birth, which is associated with the widespread use of latex in rubber tools, catheters, probes and other devices used for perioperative procedures and the presence of volatile particles of latex in the air, favoured by powdering of gloves.

The direct cause of IgE-dependent allergy is contact with volatile particles of latex. The number of reactions to this allergen is increasingly high, which is likely to be related to increased professional exposure and progress in the diagnosis of ADRs. The recent studies conducted in France reported latex-related reactions in about 12% of patients [39]. The avoidance of talc reduces the number of adverse latex reactions to 3.6% [29].

**COLLOIDS**

The number of colloid-elicited anaphylactic reactions ranges from 0.033% to 0.22% [34]. In 20% of cases, the reactions are severe and develop within 20 min after the onset of infusion. The incidence of adverse reactions to gelatine solutions is 0.852% of cases, to dextran — 0.275%, to albumin — 0.099%, and to hydroxyethyl starch — 0.0058% of cases [40, 41].

**BLOOD PREPARATIONS**

One of the mechanisms of adverse reactions after administration of blood preparations is antibody binding to the surface of erythrocytes or formation of immune complexes and activation of the complement system. The products of complement activation degranulate mast cells and basophils, release and produce mediators, which eventually leads to the anaphylactic reaction. Furthermore, complement components can directly increase the permeability of vessels and constrict smooth muscles. The IgA deficient individuals constitute a special group of patients (1/500 of the population) that can react to IgA contained in blood preparations. The anaphylactic reaction related to administration of blood preparations in this group results from the presence of anti-IgA antibodies (most likely IgE anti-IgA) [7].

**CLINICAL SYMPTOMS OF DRUG-RELATED ADVERSE REACTIONS**

Adverse reactions can develop at any stage of anaesthesia. Their severity varies from very mild, through severe failure of many systems to death [12]. During anaesthesia, such reactions can be masked by decreased arterial pressure induced by too deep anaesthesia or LA effects in block anaesthetic procedures. In general, 90% of reactions develop within several seconds or minutes after exposure to the
agent — intravenous administration of an anaesthetic or antibiotic. The location of symptoms is characterised by individual variability. They develop rapidly and affect not only the skin. Sometimes, the first symptoms are confined to the cardiovascular or respiratory system. In other cases, they are of multi-organ nature.

Once the anaphylactic symptoms gained special interest, various classifications were introduced. The first model was presented by Müller in 1966 and modified by Ring and Messmer in 1977 [41].

Still another suitably modified classification is currently recommended by the German Society of Allergology and Clinical Immunology (Table 1) and by the French Society of Anaesthesia and Intensive Care [43].

RISK FACTORS OF DRUG-RELATED ADVERSE REACTIONS

AGE

The risk of anaphylactic reactions to drugs is lower in children, which is most likely associated with immaturity of their immune systems. According to French authors, the highest incidence of anaphylactic reactions in women is observed in the fourth decade and in men in the fifth decade of life [31].

GENDER

Adverse reactions, particularly to NMBAs, affect predominantly women and the gender ratio is 8.1:2.7 [44]. Females constitute 63–70% of all ADR-suspected patients [29]. Therefore allergological tests should be conducted in all women before the anaesthesia.

DRUG ALLERGY

Based on collective analysis of factors predisposing to anaphylaxis during anaesthesia, patients may be categorised into the following groups [1]:

1. patients with documented allergy to an anaesthetic or another agent that could have been used in the perioperative period;
2. patients with symptoms corresponding to allergy during previous anaesthesia yet not allergologically tested;
3. patients with hypersensitivity symptoms during exposure to latex, irrespective of the exposure circumstances;
4. children after repeated surgical procedures, especially due to developmental spinal defects (due to widespread latex allergies);
5. patients with symptoms following consumption of avocado, kiwi, bananas, chestnuts, buckwheat, etc (i.e. allergens cross-reacting with latex).

Each unexplained, life-threatening reaction during the past anaesthetic procedure, which is likely to be the manifestation of allergy, becomes a potential risk factor of ARD following the next administration of a given preparation. Due to high incidence of cross allergies to various NMBAs, none of them should be given without earlier allergological testing [30]. The allergy to agents different from those used in anaesthesiology is not considered the risk factor of anaphylaxis during anaesthesia.

ATOPY

The term atopy is often used in relation to allergic diseases to define such conditions as asthma, hay fever, atopic dermatitis [2]. Atopy is an inherited predisposition to produce specific IgE antibodies in response to small doses of typical environmental allergens invading the human body through the respiratory or gastro-intestinal mucosa [45]. Atopy has not been recognised as a special risk factor of NMBA allergy [46]. Importantly, asthma and atopy are the factors of low predicting value of anaphylaxis during anaesthesia [18]. However, life-threatening anaphylaxis is significantly more common in patients treated with β receptor agonists, NSAIDs and acetylsalicylic acid preparations [4, 22].

DIAGNOSIS OF ALLERGIC REACTIONS DURING ANAESTHESIA

In each patient suspected of adverse reactions during anaesthesia, the possible IgE-dependent allergic reaction should be considered and attempts made to identify the agent responsible for such a reaction. Any patients who

<table>
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<th>Grade</th>
<th>Severity</th>
<th>Nature of symptoms</th>
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<tr>
<td>0°</td>
<td>Local reaction</td>
<td>Limited skin reactions</td>
</tr>
<tr>
<td>I°</td>
<td>Slight general symptoms</td>
<td>Skin: erythema, pruritus, urticaria Rhinitis, conjunctivitis General symptoms: anxiety</td>
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<tr>
<td>II°</td>
<td>Moderate general symptoms</td>
<td>Circulatory: increased heart rate, decreased blood pressure Respiratory: wheezing respiration Gastrointestinal: nausea, vomiting, stomach pain, loose stools</td>
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<tr>
<td>III°</td>
<td>Severe general symptoms</td>
<td>Circulatory: shock Respiratory: bronchospasm Central nervous system: involuntary urination/defecations</td>
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had ADR should undergo suitable diagnostic-therapeutic management. The serum samples ought to be promptly collected and the biological material tested. The allergological test performed late is to confirm the immune-mediated mechanism involved in the pathogenesis of hypersensitivity, to identify the causal factor and to search for cross allergies essential for NMBA anaphylactic reactions [46]. In the majority of cases patients are referred to a common consultation of an anaesthetist and allergologist. The diagnosis is based on history, clinical symptoms, chronology of events, results of biological material testing and skin testing. If the balance of tests is negative, some other examinations are suggested to enable further differential diagnosis.

**BIOLOGICAL MATERIAL TESTING**

Biological material testing is carried out immediately to determine the serum level of tryptase and plasma level of histamine.

Tryptase is released by activated mast cells. It is believed that elevated concentrations of this enzyme can be observed in various clinical conditions [3]. The concentration ≥ 10 µg L⁻¹ is suggestive of an allergic reaction [47]. The negative result neither justifies the abandonment of further diagnostic procedures nor excludes anaphylaxis [48]. Tryptase may also be determined in the autopsy material. In fatal cases of anaphylaxis, blood samples should be secured before the resuscitation has been completed.

Serum tryptase determinations are widely used for the diagnosis of mastocytosis. The concentration > 25 µg L⁻¹ is one of the diagnostic criteria, although it is not a specific marker of mastocytosis; thus the diagnosis should also be based on clinical features and histopathological bone marrow findings [47]. Patients with this disease are at a particular risk of perioperative hypersensitivity reactions. The most common factors inducing anaphylaxis in mastocytosis include lidocaine, procaine, morphine, etomidate, thiopentone and suxamethonium. The majority of authors recommend the suitable pre-anaesthesia choice of possibly safe agents based on skin prick testing (SPT) and intradermal testing (IDT).

Elevated levels of histamine in plasma and of methylhistamine in urine confirm excessive histamine release in vivo [8]. The threshold value is 9 nmol L⁻¹. The determinations have to be performed within one hour after first symptoms. The combined determination of histamine and tryptase levels increases the diagnostic sensitivity. Under some clinical conditions, histamine results can be false negative, which is likely to result from accelerated metabolism [49]. Such results can occur in pregnant women and patients receiving high doses of heparin, particularly during procedures with extracorporeal circulation.

The search for specific IgE antibodies mainly regards allergies to substances containing the quaternary ammonium ion, thiopentone, morphine, propofol, and latex [3,

<table>
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<th>Table 2. Recommended diagnostic management</th>
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<td><strong>Prick test (mm)</strong></td>
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<tr>
<td>Codeine/histamine</td>
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<tr>
<td>Celocurin-klorid concentrations from 50 till 10 mg mL⁻¹</td>
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<tr>
<td>Suxamethonium chloride (10 mg mL⁻¹)</td>
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<tr>
<td>Vecuronium (4 mg mL⁻¹)</td>
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<td>Pancuronium (2 mg mL⁻¹)</td>
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<td>Rocuronium (10 mg mL⁻¹)</td>
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<td>Atracurium (10 mg mL⁻¹)</td>
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<td>Mivacurium (2 mg mL⁻¹)</td>
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<td>Cisatracurium (2 mg mL⁻¹)</td>
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<td>Latex</td>
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<td>Intravenous hypnotics</td>
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<td>Morphine</td>
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<td>Opioids</td>
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<td>Local anaesthetics</td>
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PI/PO* — post-injection wheal (in mm)/oedematous wheal
when skin tests are negative [53]. The prerequisite is the patient informed consent for the procedure and associated risks. This informed consent for the procedure and associated risks. This method was used to determine asIgE against latex show the 80% sensitivity and 50–90% specificity [50].

Intradural tests (IDTs) or skin prick tests (SPTs) should be performed 4–6 weeks after the allergic reaction, which corresponds to the period of optimal reactivity to the substances analysed [51]. Noteworthy, all preparations used before and during anaesthesia should be included and the time between their administration and occurrence of symptoms considered. Anti-histamine drugs should be appropriately earlier withdrawn as they reduce the skin reactivity. In 1985, IDT was recommended for hypersensitivity testing to all available NMBA [51]. The incremental dilutions should be used to disclose cross allergy of moderate severity. The diagnostic methods and threshold values of tests were standardised for many anaesthetic agents to avoid false positive results associated with non-specific release of histamine (Table 2) [31].

The overall evaluation of results should consider the negative control (test with 0.9% NaCl) and positive control (tests with histamine and codeine), determining normal skin reactivity. It ought to be assumed that any agent or substance administered during anaesthesia could be responsible to allergic reactions. If one muscle relaxant was used, tests should involve all preparations from this group [23], which enables to determine the recommendations for NMBA choices for future anaesthetic procedures. The interpretation of IDT in search for cross allergies to atracurium and mivacurium is complicated due to non-specific release of histamine [9].

Serum asIgE can be determined later if the test was not performed during the ongoing reaction or its result was negative. The method of determinations of histamine released by peripheral blood leucocytes stimulated in vitro by the relaxants studied shows the sensitivity of 71% and is useful for identifying the cause of reaction when asIgE determinations are infeasible. Moreover, this method is of importance to evaluate cross reactivity to relaxants for future anaesthesias. Some other useful methods include evaluation of markers of basophil activation using flow cytometry and determination of serotonin, eosinophil cationic protein and leukotriene C4 levels. These methods, however, are not recommended for everyday practice [52].

Another solution is drug re-exposure test, yet its indications are very limited. The prerequisite is the patient informed consent for the procedure and associated risks. This test enables to eliminate allergy to LAs, latex, and antibiotics when skin tests are negative [53].

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35. Renz CL, Laroche D, Thurm JD: Tryptase levels are not increased during vancomycin induced anaphylactoid reactions. Anesthesiology 1998; 89: 620–625.


