

Skin Prick Test in the Diagnosis of Allergy in the Perioperative Period – 8 Year Experience

Grażyna Michalska-Krzanowska*

Department of Anaesthesiology and Intensive Care, SPS Health Care Centre "Zdroje", Szczecin, Poland

Abstract

Epidemiological studies indicate an increase in allergies in the perioperative period. Some allergens can be life-threatening. One of the most difficult and time-consuming issues in practical allergology is to diagnose the reaction-inducing agent, particularly in the perioperative period. The paper presents various aspects of the diagnosis of allergy highlighting the usefulness of skin prick testing. The study involved 52 patients (42 women and 10 men). They were selected out of 72,380 patients anaesthetized for surgeries in 2003 and 2010. The physical examination of patients who experienced allergy determined the location, extent and severity of side effects. The tests were always conducted after inserting an intravenous catheter, under full safety conditions. A positive reaction after allergen application occurred in the form of a wheal of 3 mm or more in diameter and erythema. Patients were subjected to skin prick tests and intradermal tests using all anaesthetic drugs, including NMBA, applied during anaesthesia (according to the anaesthesia protocol). Four patients (7.69 %) had positive SPT to latex, which showed clearly that it was the causative factor of the reaction. One of the patients (1.92 %) had positive SPT to atracurium, the others to augmentin and pethidine. Three patients (5.76%) had positive SPT to NMBA (atracurium, cisatracurium, rocuronium) (wheal size greater than 3 mm compared to the negative control). Positive intradermal test results to NMBA were identified in 27 patients (51.92 %). Patients received a written notice of the occurrence of suspected anaphylactic reaction during anaesthesia, the potential cause and the implemented therapeutic procedure. Increased dermographism made the skin tests in patients difficult to interpret, and therefore the following results were also taken into account: tryptase, specific IgE and clinical symptoms manifested during anaesthesia, recorded in patient records. Detailed history, skin prick testing, laboratory methods, and double-blind placebo-controlled challenges are still the gold standard for the diagnosis of hypersensitivity, although sometimes results can lead to difficulties of interpretation or can be even misleading.

Keywords: Allergy; Anaphylaxis; Anaesthesia; Diagnosis; Skin tests

Introduction

Allergy in the perioperative period is an important clinical problem. Unfortunately, due to the lack of guidelines for the recognition and diagnosis of allergy/hypersensitivity, there are still no epidemiological data on this issue. The European Academy of Allergy and Clinical Immunology (EAACI) and the World Health Organization propose that anaphylactic reactions be classified as allergic anaphylaxis (immune) rather than non-allergic (known to data as anaphylactoid or pseudo anaphylactic) [1]. One of the most difficult and time-consuming issues in clinical practice is to diagnose the reaction-inducing agent, particularly in the perioperative period. Diagnosing an allergic reaction and distinguishing it from other symptoms occurring during anaesthesia is difficult, since almost all symptoms of allergic reactions are also common side-effects of anaesthesia, e.g. hypotension at induction of anaesthesia, tachycardia at intubation and start of surgery, and bronchospasm after mechanical stimulation of the airways. This may explain why an allergen was not found in a substantial number of the 'incorrect suggestion' cases. Another reason why an allergen was not found in these cases may be that some of the reactions resulted from non-specific histamine release, which has a non-IgE-mediated mechanism and may lead to a negative result on conventional allergy investigation. The usefulness of skin prick testing (SPT) in the diagnosis of allergy is still debated. Skin testing can be performed using scarification tests, skin prick tests, intradermal tests, prick-by-prick tests, patch tests and contact tests. Skin prick testing has many advantages and has been most common for several years. It has been shown, among other things, that results of skin prick tests correlate better with the presence and severity of clinical symptoms than results of intradermal tests or specific IgE antibody titres in serum [2-4]. Because of the minimal risk of systemic

reactions (anaphylaxis risk up to 0.04%), skin prick testing allows for performing more tests at one application than intradermal testing [5,6]. As skin prick testing is often the only method used in order to confirm or rule out allergy (they determine the clinical diagnosis and possible treatment), it should be remembered that it is easy neither to perform them nor to interpret results. Improper testing techniques (pricks made too close to each other, bleeding or too superficial penetration of the epidermis), poor quality of materials (non-standardized or poorly stored allergen extracts) and the remaining factors disrupting the mechanisms of immune reactions in the skin (a history of infections, the use of antihistamines or poor diet) may yield false negative or false positive results [2,7,8].

Skin testing is minimally invasive, and when properly performed, is characterized by reliable reproducibility, easy quantification of results and the ability to recognize different allergens during a diagnostic session. Prick and intradermal tests are generally more sensitive than in vitro techniques. SPT performed alone or in combination with in vitro testing allows identification of allergens, which are the causative agents of an adverse drug reaction (ADR) during anaesthesia and in the perioperative period [especially allergy to beta-lactam antibiotics and

*Corresponding author: Grażyna Michalska-Krzanowska, Ul. Stroma 4c, 70-004 Szczecin, Poland, Tel: 48602795055; E-mail: grazyna195@op.pl

Received July 05, 2014; Accepted August 12, 2014; Published August 19, 2014

Citation: Michalska-Krzanowska G (2014) Skin Prick Test in the Diagnosis of Allergy in the Perioperative Period – 8 Year Experience. J Allergy Ther 5: 188. doi:10.4172/2155-6121.1000188

Copyright: © 2014 Michalska-Krzanowska G. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

local anaesthetics (LA)]. However, the reliability of these tests depends on a number of factors. In the case of skin testing, it is important that the technician performing the skin tests and the clinician ordering or interpreting these tests are aware of the advantages and pitfalls of the type of skin testing, the device used, the location of the tests on the body, the extracts used and the potential for suppression of the skin response by medications used to treat allergies. As for *in vitro* testing, it is imperative that quality assurance standards be met. Quality requirements include calibration of the assay, training and experience of the laboratory technician and the use of quality allergens in the solid phase [7,9,10]. As in any other diagnostic test, it is of paramount importance that the clinician considers the positive and negative predictive value of the tests performed. These tests should always be treated as adjuncts to the medical history and physical examination in formulating the diagnosis in each individual case, bearing in mind that both test types can yield false positive or, less commonly and false negative results. Skin prick testing often fails in the search for inhalant allergens of clinical importance, because we know that the positive predictive factor for SPT is less than 50%. In addition, the usefulness of SPT in the diagnosis of delayed-type allergy is still debated. The immunological mechanism is important as skin prick testing identifies only IgE-mediated hypersensitivity. Lack of skin changes does not necessarily exclude a drug as the allergic trigger. The aim of the study is to assess the relevance and usefulness of SPT in the diagnosis of allergy in the perioperative period. Our investigations indicated that combining skin tests with IgE and Mast Cell Tryptase assays may help improve accuracy. This paper was to report allergic reactions in the perioperative period that were documented with a clear and detailed medical history (description of the reaction) and skin tests. The evaluation was conducted in Poland (Szczecin and Poznań) over a period of 8 years.

Materials and Methods

The study involved 52 patients (42 women and 10 men). They were selected out of 72,380 patients anaesthetized for surgery in 2003 and 2010. The study was approved by The Szczecin Medical University Ethics and Research Committee. The tests were conducted in patients admitted to the Wards of Anaesthesiology in Szczecin and Poznań. The age of the patients ranged from 39 ± 7.75 years and their weights were in the range of 68.58 ± of 10.14 kg. During anaesthesia, suspected anaphylactic reactions occurred in these patients. This represented 0.07% of the total population of anaesthetized patients in the selected hospitals. Depending on the applied anaesthetic drugs, patients were divided into two groups. Group I (n=40) included patients anesthetized using neuromuscular blocking agents (NMBA). Group II (n=12) included patients anesthetized without the use of NMBA. People with hyper-reactivity of the tracheobronchial tree, neuromuscular diseases, kidney diseases and liver failure were excluded from the study group.

The physical examination of patients who experienced ADR determined the location, extent and severity of side effects. ADR

severity during anaesthesia was assessed based on the symptom classification system recommended by the Ring and Messmer severity scale (Table 1) [11].

For the purposes of SPT determination, the author has made a protocol of skin prick tests. The protocol includes: a patient eligibility form (Annexure), information about the materials needed for skin prick testing, instructions on how to perform tests and interpret results, and an allergy skin test report. On the day of the tests, and prior to them, the patient was asked to respond to the questions in the form annexed to the protocol. This was to exclude any reasons preventing the testing and to obtain information necessary for the evaluation of results. Questions in this form are divided into sections A and B. If the patient gave a positive answer to even one of the questions in Section A, the test could not be performed on a given day. The testing technician explained the reasons why it could not be performed, informed the patient how to properly prepare for the test and set another testing date. If answers to all the questions in Section A were negative, the patient was accepted for testing on a given day. The patient should then answer questions from Section B. The answers did not affect the change of the testing date; they were informative and helped to conduct the tests and interpret results.

The extent of skin lesions that occurred in an anaesthetized patient as a symptom of ADR was determined on the skin surface divided into 12 areas. The skin lesion coverage was determined in percentage. At 1-10% of coverage, the patient received 1 point, at 11-30 % -2 points, and at 31-100 %-3 points. In this way, the point indicator of the extent of skin lesions was obtained. The reaction was documented in the patient records, anaesthesia protocol and a questionnaire specially developed by the author. A copy of the questionnaire was attached to the patient's anaesthetic chart. The questionnaire was available at each anaesthesia workstation. It contained, among others, questions about symptoms and their connection with any previous anaesthesia and the reproducibility of the observed episodes, as well as the symptoms of anaphylactic or acute urticaria after the administration of drugs in the perioperative period.

Patients received a written notice of the occurrence of suspected anaphylactic reaction during anaesthesia, the potential cause and the implemented therapeutic procedure. Subsequently, they were diagnosed for allergy to determine the sensitizing allergen and exclude it from any further anaesthetic or therapeutic procedures. Adverse reactions occurred in patients in the operating room and/or recovery room. Patients were routinely prepared for anaesthesia during the anaesthetic visit on the day before the operation. A detailed treatment plan to be implemented in the event of an allergic reaction was based on the generally accepted standards of therapeutic intervention. The aim of ADR treatment was to interrupt the exposure to a sensitizing allergen, to minimize the effects of mediators and to limit their production and release. One hour after the onset of symptoms, 10 ml of blood was collected to determine the levels of Mast Cell Tryptase (MCT). Blood

Reaction assessment scale (0°-IV°)	Severity of reaction symptoms	Nature of symptoms
0°	Local reaction	Limited skin reaction
I°	General symptoms: light	Skin: erythema, pruritus, urticaria, rhinitis, conjunctivitis General symptoms: anxiety
II°	General symptoms: moderate	Circulatory: heart rate ↑, RR ↓; breathing: wheezing; gastrointestinal: nausea, vomiting, abdominal pain, loose stools
III°	General symptoms: severe	Circulatory: shock; respiratory: bronchial obstruction; the central nervous system: involuntary urination/stool
IV°	Acute circulatory-respiratory failure	Cardiac arrest, respiratory arrest

Table 1: Symptom classification system recommended by the German Society for Allergy and Clinical Immunology (DGAI).

Drug name	Drug concentration (mg/ml)	Skin prick testing Dilution	Intradermal testing Dilution			
			Atracurium	10	1:10	1:10,000
Cis-Atracurium	2	1:01	1:10,000	1:1,000	0.1111111	X
Mivacurium	2	1:10	1:10,000	1:1,000	X	X
Pancuronium	2	1:01	1:10,000	1:1,000	0.1111111	1:10
Rocuronium	10	1:01	1:10,000	1:1,000	0.1111111	X
Suxamethonium	50	1:05	1:10,000	1:1,000	0.3888889	X
Vecuronium	4	1:01	1:10,000	1:1,000	0.1111111	1:10
Etomidate	2	1:01	1:10,000	1:1,000	0.1111111	1:10
Midazolam	5	1:01	1:10,000	1:1,000	0.1111111	1:10
Propofol	10	1:01	1:10,000	1:1,000	0.1111111	1:10
Thiopental	25	1:01	1:10,000	1:1,000	0.1111111	1:10
Other e.g., Morphine	10	1:10	1:10,000	X	X	X

Table 2: Concentrations of NMBAs and other anaesthetics optimal for skin testing.



Figure 1: Standard panel of drugs.

samples were sent to a laboratory where they were centrifuged, and the obtained sera were frozen.

Patient Allergy Assessment

After 4-6 weeks from the time of the reaction occurrence, patients were asked to come to the Department of Allergology, to have skin tests done according to standardized procedures [12]. The tests were always conducted after inserting an intravenous catheter, under full safety conditions. Patients were subjected to skin prick tests and intradermal tests using all anaesthetic drugs, including NMBAs, applied during anaesthesia (according to the anaesthesia protocol). Threshold concentrations were adopted for the individual drugs to avoid false positive results related to non-specific histamine release. Skin prick testing was performed using atracurium, mivacurium and morphine at a dilution of 1:10, and the other drugs at a dilution of 1:1. Intradermal testing was performed starting from the dilution of 1:10,000, through 1:1,000, 1:100 and 1:10 (threshold dilutions: for atracurium and mivacurium – 1:1,000, for suxamethonium, rocuronium and cisatracurium – 1:100) (Table 2).

Skin Prick Testing (SPT)

Skin prick testing was performed following the standardized procedure [1,2,12-14].

The skin prick tests were performed on the volar side of the forearm at a distance of not less than 5 cm from the wrist and 3 cm from the

elbow. It was possible to carry out the tests only on unaffected skin. Skin disinfectants did not include strong antiseptics or alcohol. Before testing, the patient could wash the skin of the forearm with soap, and then they had to wait for at least two minutes to restore normal blood supply. The skin was symbolically and legibly coded with a marker pen to identify the solutions to be tested. One drop of each tested solution was placed on the marked skin, using a dispenser attached to each tested solution, at a minimum distance of 3 cm between the test sites. At the end of the test series, control solutions were applied: first, negative control (0.9% NaCl solution), followed by positive control (histamine solution 1/1,000). The superficial layer of the skin was punctured using a tip of a Morrow Brown lancet (1 mm blade length), at the maximum acute angle. Bleeding disqualified the trial. Each prick was done with a new lancet. The tested solutions were removed after 5-10 minutes of application using a cotton swab. If a rapid exacerbation of an allergic reaction was observed at the puncture site, the solution was removed immediately. SPT were performed in all patients using a standard panel of drugs (histamine/codeine and 0.9% NaCl solutions) (Figure 1). In addition, drugs administered individually to patients during anaesthesia were tested. A positive reaction after allergen application occurred in the form of a wheal of 3 mm or more in diameter and erythema. To determine the size of the wheals, their diameters were measured (using a transparent ruler): the longest diameter and its perpendicular diameter. The measurements were summed and then divided by 2 in order to obtain an average wheal diameter.

The obtained value was compared with the mean diameter of the histamine wheal and the result was expressed on a '+' scale (Table 3).

In addition to the '+' scale, the mean diameter of each wheal was measured and recorded in millimetres. The mean diameters of positive and negative controls were always given in the test report form. In the case of a wheal induced by negative controls, 0.9% NaCl solution was applied to the other forearm. If the positive response to the negative control fluid was confirmed, in the assessment of reaction to allergen solutions, the mean allergic and histamine wheal diameters had to be reduced by the average negative control wheal diameter and only then compared with the histamine wheal.

Test results were read after 15-20 minutes of application. At that time, the course of reaction was controlled several times, especially when the patient had severe allergic reactions.

In addition, skin prick tests were performed in all patients using latex extracts.

Scale	Result
0	The allergic reaction was equal to the negative control reaction
+	The mean wheal diameter was higher than the allergenic reaction to the negative control fluid, and less than half of the mean histamine wheal diameter
++	The mean allergic wheal diameter was equal to or greater than half of the mean histamine wheal diameter
+++	The mean allergic wheal diameter was equal to or greater than the mean histamine wheal diameter
++++	The mean allergic wheal diameter was at least two-fold greater than the mean histamine wheal diameter or every reaction with pseudopodia

Another plus was added with each doubling of the mean allergic wheal diameter in relation to the histamine reaction.

Table 3: The results of allergic reaction using the '+' scale.

Intradermal Testing (IDT)

Intradermal testing was performed in patients with negative prick test results. The volume of 0.02-0.05 ml of drug solution in saline was used for intradermal testing, which corresponds to a wheal of 3 mm in diameter. In accordance with the recommendation of the experts of the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO), a test result was positive when the difference between the diameter of the wheal which appeared immediately after pricking the skin and assessed after 20 minutes was greater than or equal to 3 mm. [10,13,14]

Determination of antigen-specific IgE (asIgE)

Antigen-specific IgE antibodies were measured in blood serum using the methods Cap- RAST, Pharmacia and Alastat, Diagnostic Product Corporation. The author has chosen the most sensitive of the available methods for determining specific IgE in serum. Allergens against which specific IgE were determined were individually selected, depending on interviews and skin prick test results. Allergens such as Hev b 6.02 (Heweina) and Hev b1 (agent responsible for the extensibility of rubber), that most commonly cause allergy in health care workers, were selected to identify latex allergens. The sensitivity of the method of specific IgE determination in cases of latex allergy was very high and exceeded 90%. Test results were expressed in KU/l and interpreted according to the ranges contained in the scale specified by the manufacturer. Specific IgE class II or more was interpreted as a positive test result (Class I: 0.35-0.69 IU/l Class II: 0.7-3.49 IU/L, Class III: 3.5-17.49 IU/l, Class IV: 17.5-51.9 IU/l, Class V: 52-99 IU/l; class VI: > 99 IU/l).

Determination of serum Mast Cell Tryptase (MCT)

After collecting a certain number of blood samples by a radioimmunoassay method using UniCap (Pharmacia, Uppsala, Sweden), MCT was measured. Normal levels are in the range of 1-10 µg/L. The author assumed that levels greater than 10.5 µg/l indicated an allergic reaction [15,16].

Results

A point estimate indicated that the proportion of anaphylaxis among the studied group of patients was in the range of 0.072 % ± 0.01%. The study showed that this proportion in the examined population was 7.2 per 10,000 cases of anaesthesia (±1 in 10,000 – in the studied sample it was exactly 7.2 per 10,000 cases of anaesthesia). Most of the adverse reactions – 80.76 % (n=42) occurred in women, and 19.23% (n=10) in men. Depending on age, nine reactions occurred in the range of 20-29 years: 30-39: 17; 40-49: 12; 50-59: 9; 60-69: 3; 70-79: 2. The largest number of reactions was identified in women in the fourth decade of life and in men in the sixth decade of life. All the reactions are potentially life-threatening and should be evaluated and its treatment instituted when necessary. Fifty-two patients (0.07%) with adverse reactions during anaesthesia were subjected to further

analysis to identify the suspected sensitizing substance. The patients were checked for their eligibility for the planned anaesthesia before various surgical procedures based the ASA I scale (American Society of Anaesthesiology) (65%) and ASA II/III scale (35%). In the course of anaesthesia, various other substances were administered that could potentially be responsible for the occurrence of ADR. In the questionnaire filled in before anaesthesia, almost half of the patients (25/52) reported one or more previous surgeries in general or local anaesthesia. Twenty-seven patients underwent no previous surgical interventions, and the allergic reaction was suspected in 13 of them. The NMBAs suspected of causing ADR included antibiotic in 3 cases, thiopental in 5 cases and opioids in 2 cases. In contrast, only 4 patients enrolled in the study, with previous surgeries, presented symptoms of ADR after certain anaesthetics. Two of them turned out to be NMBA-positive (atracurium, rocuronium), one patient reported an adverse reaction to LA, while another pointed to metohexital (Brietal) as the causative agent of ADR. Earlier ADRs after drugs not associated with anaesthesia were reported by 10 patients. Taking into account the phase of anaesthesia, 39 ADRs appeared at the time of induction, 10 during anaesthesia, 1 during recovery from anaesthesia and 2 after pre-treatment. In 48 of 52 cases (92.30%), substances potentially responsible for adverse reactions were suggested. They were confirmed in a full allergy examination only in 13 cases (25%). In the other cases, test results were not conclusive and could indicate a different drug as the causative agent. In 10 cases (19.23%), this was partially confirmed, because the substance suspected of causing ADR was not confirmed in the allergy examination and another substance causing ADR was detected. Two patients (3.84%) had systemic mastocytosis features. One of them died of extensive post-stroke changes in the course of diagnosis. The patient was treated for cardiac ailments, unstable blood pressure and paroxysmal atrial fibrillation. During the hospitalization, a cerebrovascular disorder occurred, and a computed tomography of the head showed extensive changes after ischemic stroke. The second patient was referred to the Clinic of Haematology for further diagnosis.

It was of paramount importance to identify the onset, course, duration and location of symptoms. It was also crucial to observe the temporal relationship between the onset of symptoms and the administration of a specific preparation suspected of causing adverse reactions. A careful interview, the form and the preoperative anaesthetic questionnaire made it possible to identify previous exposures to the suspected drug and get information on all drugs used in the recent period. Information obtained in an interview with the patient provided valuable information regarding risk factors, atopy, other diseases and possible early occurrence of drug-induced allergic reactions. Any drug could potentially cause an adverse reaction in a patient. On the other hand, the same drug could cause a variety of symptoms, while a range of drugs could induce the same response. Diagnosing only on the basis of a subjective test was very difficult, if not impossible, and could be subject to a high percentage of false positive diagnoses. Hypersensitivity to the drug was highly probable when the signs

Number of patients reporting ADR	MCT [$\mu\text{g/L}$]	SPT	asIgE[KU/L]
11(21.15%)	High level	Positive	Positive
2(3.84%)	High level	Positive	Negative
2(3.84%)	Low level	Negative	Positive (NMBA, Morphine)
37(71.15%)	Low level	Negative (With positive IDT: 51.92%)	Negative

Table 4: The results of MCT, SPT and as IgE.



Figure 2: Positive SPT to latex.



Figure 3: Urticaria wheal in SPT to tracrium after 15 minutes of exposure to this agent.

and symptoms corresponded to the manifestation of immune drug reaction, and there was a definite temporal relationship between taking the drug and the onset of symptoms. Many of the drugs or substances used in perianaesthesia can provoke adverse reactions related to their pharmacological properties (usually dose-dependent), or unrelated to the same (less dose-dependent), with the latter corresponding to: intolerance, idiosyncratic and anaphylactic reactions (immune or non-immune). The interview with the patient was supplemented by detailed clinical examination, including all systems, and basic laboratory tests (hematology, blood chemistry, and urinalysis), imaging and ECG. Before anaesthesia, each patient was subjected to a full range of basic tests. The levels of Mast Cell Tryptase (MCT) and specific IgE (against the selected drug allergens) were additionally determined in the serum of all patients with adverse reactions.

Results of serum Mast Cell Tryptase determination (MCT)

Tryptase levels were determined in 52 patients with ADR. In 10 of them (19.23%), MCT control values after the resolution of ADR symptoms were not detected. One of the reasons was that patients did not turn up for tests, while additional health complications did not allow other patients to have control tests. Control tests performed in a group of 42 patients without clinical evidence of mast cell stimulation showed that mean tryptase levels in serum were in the range of $1.23 \pm 0.12 \mu\text{g/L}$. There was no difference in the reference values relating to gender or age in the study group. In 9 patients (17.30%), MCT levels hovered above $10 \mu\text{g/L}$. In 6 of them (11.53%), the causative agent of the reaction was suggested and confirmed (plasma, augmentin, meropenem, pethidine, thiopental, brietal). In one case (1.92%), many agents were suspected of inducing the reaction, but none was confirmed. In 2 patients (3.84%), MCT levels were high at each time point of measurement, regardless of exposure to the agent suspected of causing ADR. These patients were referred to further diagnostic tests for mastocytosis. MCT levels were consistently elevated in 4 patients (7.69%), and the drugs suggested and confirmed as responsible for ADR were successively: morphine, thiopental, pethidine and plasma. In 3 patients (5.76%) with severe anaphylactic reaction, MCT levels were normal, just as in patients with type I°/II° ADR symptoms on the symptom severity scale. In these cases skin tests were very useful.

Results of determination of serum antigen-specific immunoglobulin IgE antibodies against selected allergens in ADR patients

Methods for determination of specific IgE were calibrated using a standard IgE WHO 75/502, and the results were expressed in quantitative units U/ml (kU/l), where 1 U corresponded to 2.44 mg IE. The analytical sensitivity of the methods for the determination of IgE was 0.1- 0.35 U/ml. Due to the high sensitivity and specificity of the tests, the author determined the level of specific IgE once. Specific IgE against selected drug allergens were measured in the serum of ADR patients. An analysis of the results of specific IgE determination in 10 patients (19.23%) showed that the mean values were $2.57 \pm 1.21 \text{ KU/L}$. In 2 patients (3.84%), an increase in IgE levels did not correlate with simultaneous positive skin prick test results. Specific IgE antibodies to latex were confirmed in 4 patients (7.69%), to amoxicillin with clavulanic acid in 1 patient (1.92%), to morphine in 1 patient (1.92%), to quaternary ammonium ions [NMBA- (PAPPC-RIA)] in 3 patients (5.76%) (atracurium, cisatracurium, rocuronium) and to thiopental in 2 patients (3.84%). Suxamethonium-specific IgE was negative in all patients.

Results of skin reactivity in ADR patients

Skin prick testing (SPT) and intradermal testing (IDR) were used in the diagnosis of ADR (Table 4).

In 4 patients (7.69%), positive SPT results showed clearly that latex was the causative factor of the reaction (Figures 2 and 3). One of the patients (1.92%) was SPT positive to atracurium (Figure 4), while the other subjects were SPT positive to augmentin and pethidine (Figure 5). Positive SPT to NMBA (wheal size greater than 3 mm compared to the negative control) was observed in 3 patients (5.76%) (atracurium, cisatracurium, rocuronium). Positive intradermal test results to NMBA occurred in 27 patients (51.92%). Increased dermatographism caused that the skin tests in patients were difficult to interpret, and therefore the following results were also taken into account: MCT, specific IgE and clinical symptoms manifested during anaesthesia, recorded in patient records. Figures 6 and 7 show a diagram of skin



Figure 4: Positive SPT to augmentin.



Figure 5: Skin tests used to identify an agent causing anaphylaxis during anaesthesia.



Figure 6: Skin tests to drugs administered during anaesthesia (after 15 minutes).

tests performed to identify the causative agent of ADR in a patient with severe anaphylaxis during anaesthesia. There was a positive reaction to cisatracurium (Nimbex), which was used to anesthetize the patient. An allergic reaction to mivacurium also occurred in the same patient, and therefore these two muscle relaxants must not be used as anaesthetics in the future.

Cross-reactivity to NMBA

Cross-reactivity is of great clinical importance, because every

NMBA is able to bridge specific IgE antibodies on the cell surface and produce anaphylactic reaction. In view of the well-known risk of cross-reactivity, the author made a detailed IDR interpretation in the course of skin tests, in the search for cross-sensitization in a group of 3 patients. The patients presented symptoms of anaphylaxis after the application of atracurium, cisatracurium and rocuronium. Only 1 patient who was positive to vecuronium, which was confirmed by a full allergy examination, was particularly prone to cross-reactions. In this patient, positive IDR results confirmed cross-sensitization to pancuronium, atracurium, cisatracurium and rocuronium. Intradermal tests were performed using increasingly diluted NMBAs to reveal the cross-sensitization of moderate severity. Positive SPT to succinylcholine was doubtful, while intradermal test results to succinylcholine were negative.

Discussion

The diagnosis of anaphylactic reactions in the study was determined based on medical records, interviews, the patient eligibility form, the questionnaire developed for the needs of patients suspected of ADR, clinical symptoms, skin tests, specific IgE and MCT determination and in exceptional cases, specific challenges. Different diagnostic protocols have been proposed in the literature, but it would seem that both clinical history and skin testing results are necessary to confirm ADR in perioperative period. This is why we intentionally decided to report only cases with both a clear clinical history and a positive skin test result. The interview was a source of key information about the symptoms of hypersensitivity, which might correspond to IgE-mediated allergy, sensitizing and accompanying agents or experienced atopic reactions and diseases. The clinical history should be regarded as preliminary screening, while the task of skin tests or in vitro tests was to confirm the information gathered in the interview. Correct identification of the substance responsible for adverse reaction during anaesthesia was extremely complicated. In fact, any drug can cause an adverse reaction, the symptoms of which worsen the patient's condition, make the treatment difficult and can be life-threatening in extreme situations. Indeed a number of different factors can affect the course of ADR. The clinical picture of ADR can be very diverse. The author's own study has shown that the percentage of ADR suspected of inducing anaphylaxis was 7.2 per 10,000 cases of anaesthesia (± 1 in 10,000). Mortality amounted to $0.003\% \pm 0.002$. The analysis of other critical events occurring during anaesthesia indicates a gradual decline in their numbers over the past 20 years. On the basis of literature data, it can be concluded that of the total number of 503 causes of critical events relating to the respiratory system, responsible for death or irreversible damage to the central nervous system (CNS), 115 cases



Figure 7: Skin test procedure.

related to difficult intubation, 111 – inadequate pulmonary ventilation, and 66 – unrecognized oesophageal intubation [17-19]. Among these three types of dangerous adverse events, the number of cases of inadequate pulmonary ventilation and esophageal intubation decreased substantially in 1990 (9%) compared with 1980 (25%), as a result of the introduction of standardized procedures and the obligation to equip an anaesthesia workstation with a pulse oximeter and capnometer. Over the 80s, 90s and until the twenty-first century, difficult intubation, which is the cause of death or CNS injury, has been maintained at the level of 8-9% (8.8 per 10,000 cases of anaesthesia) of all critical events associated with difficult airways [18-20]. Comparing these figures with the ADR values presented by the author on the basis of her own observations, it can be concluded that from the epidemiological point of view, the events are comparable, and the weight of the ADR issue in the perioperative period should be stressed. Our findings indicate the validity of the use of skin testing in patients anaesthetized for surgery and in the perioperative period. Until recently, it was believed that the combined use of IDR with SPT and specific IgE would eliminate the need to perform difficult and laborious allergen challenges, but despite the high rate of positive prediction, it has been found that it is not a sufficient reason to abandon challenge tests [21]. It has been shown that some patients have a negative specific IgE and positive SPT to the same allergens, which may result from a local production of IgE in the skin. According to the literature, skin tests are most useful in patients with atopic dermatitis, while in some cases the authors emphasize their legitimacy in allergy with diverse clinical manifestations, not necessarily skin allergy [22-24]. Intradermal testing is far more sensitive than prick testing, which means that it requires about 1000-fold less concentrated extracts than those used for prick testing to achieve a similar response. Although direct comparisons indicate that intradermal testing is more reproducible than percutaneous testing, there are many factors that favour the routine use of percutaneous allergy tests, including economy of time, patient comfort and patient safety. In turn, the higher sensitivity of intradermal skin tests does not usually offer added benefit, since the results of skin prick tests performed with potent extracts are of sufficient sensitivity for use in clinical practice. Researchers show that in the future, it will be much more important to study changes in skin reactivity using SPT [25,26]. It will be necessary to repeat SPTs in the same person, and compare the resulting reactions. One method is to refer test results to changes in the concentrations of allergen extracts that cause specific reactions, the lowest concentration causing a response interpreted as (+), or a change in the concentrations of extracts causing the same reaction.

Skin test results are often reported by clinicians in semiquantitative terms. They may record results only as positive or negative, or express them on a 0 to 4+ scale without any indication of the size of the reactions that these numbers represent. However, allergy patients may have to change their allergist for numerous reasons, and it is important that records of prior allergy testing be interpretable by the receiving physician. At the very least, a record of skin testing should contain sufficient information to allow another physician to interpret the results and avoid the need to repeat skin testing. Standardized forms have been developed and are available through the American Academy of Allergy Asthma and Immunology website (for an example AAAAI's Skin Test and Immunotherapy Forms).

Although the area of the wheal and erythema are the most accurate measurements, the longest diameter or two diameters at right angles to each other correlate with area ($r > 0.9$). The importance of performing such measurements is exemplified by McCann and Ownby in which allergists were asked to interpret photographs of skin test reactions [27].

The scoring and interpretation of the skin test results varied greatly. The authors of this study reinforce the idea that the most reliable method of reporting a skin test reaction is to measure and record the reaction size. At the very minimum, skin test results should be graded 0 to 4+, and the criteria for each grade of reaction clearly stated along with the skin test results.

Various investigators suggest different criteria for interpreting a skin test response as positive. To assess the reliability of different means of interpreting the results of skin prick testing, Vanto and colleagues studied a group of 202 children sensitive to dogs [28]. A determination of sensitivity to dog was based on a composite score derived from the history, RAST, and bronchial or conjunctival challenges. Although in this study the overall efficacy was greatest with the histamine reference method (in which the allergy skin test response is compared to a histamine control, with a positive response considered to be a response at least as great as that of the histamine control), maximal sensitivity was achieved when using a cut off of a wheal 3 mm. If a clinician wishes to maximize sensitivity, the latter criterion would be most useful; however, adjustment must be made for the device used. Therefore, the criteria for a positive test should be the larger of: 1) 3 mm mean wheal diameter or 2) equal to or greater than the 99th percentile reaction with that device at negative control sites. Although purely research conditions assume and enable to perform allergen challenges to confirm the allergic background of ADR in the perioperative period, detailed history and physical examination should be the standard medical diagnostic tools. Skin testing correlates with results of allergen challenges, taking into account non-specific airway responsiveness [29]. Allergen challenges in selected clinical situations are the "gold standard" for the confirmation of allergies. These can be performed as open challenges or in a single- or double-blind fashion. Allergen challenges are not without risk and thus require that appropriate supportive care be available. A number of studies demonstrate that the magnitude of the in vitro test or the skin test reaction size may be useful in determining the utility of performing an allergen challenge [30]. Skin test results generally correspond to the results of in vivo allergen challenges. On the other hand, in vitro tests provide an alternative, a back-up tool for diagnosing anaphylaxis.

The study results indicate that skin testing may be a useful additional tool in the diagnosis of allergy in patients in the perioperative period. A correct diagnosis of allergy helps to verify an allergen. In turn, elimination of the agent suspected of inducing anaphylaxis in the perioperative period in patients with hypersensitivity can cause both a reduction in the severity of symptoms and decline in the severity of the disease, thus mitigating the undesirable reaction. Although SPTs increase the accuracy of diagnosis, still challenge tests cannot be abandoned, as they continue to be an indispensable and essential tool in the diagnosis of allergies. The evaluation of the usefulness of SPT, however, requires further research.

Conclusion

Diagnostic testing is an essential tool for the evaluation of the allergic patient. A number of variables should be controlled in order to obtain more reliable results of skin tests and improve the predictive values of allergic skin testing. Another necessary condition is that allergists verify skin test results by conducting proficiency testing. Furthermore, the results must be properly documented to make them easily understandable by others. Similar standards must be applied to in vitro testing; as in the case of skin testing, it is imperative that the ordering physician be familiar with the operating characteristics that the in vitro lab employs.

References

- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, et al. (2004) Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 113: 832-836.
- Dreborg S, Backman A, Basomba A, Bousquet J, Dieges P et al. (1989) Skin tests used in type I allergy testing. Position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 44: 1-69
- Brown WG, Halonen MJ, Kaltenborn WT, Barbee RA (1979) The relationship of respiratory allergy, skin test reactivity, and serum IgE in a community population sample. *J Allergy Clin Immunol* 63: 328-335.
- Alergiczny niezbyt nosa i jego wpływ na astmę. Raport ARIA(2002) Med Prakt wydanie specjalne 7-20.
- Wisniewska-Barcz B, Orlowska E (2001) Testy skórne w diagnostyce alergologicznej. *Alergol Wspólcz* 4: 15-30
- Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA (1993) Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 92: 6-15.
- Bernstein IL, Storms WW (1995) Practice parameters for allergy diagnostic testing. Joint Task Force on Practice Parameters for the Diagnosis and Treatment of Asthma. The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 75: 543-625
- Simons FE, Simons KJ (1999) Clinical pharmacology of new histamine H1 receptor antagonists. *Clin Pharmacokinet* 36: 329-352.
- Demoly P, Bousquet J, Manderscheid JC, Dreborg S, Dhivert H, et al. (1991) Precision of skin prick and puncture tests with nine methods. *J Allergy Clin Immunol* 88: 758-762.
- [No authors listed] (1993) Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 48: 48-82.
- Tryba M, Ahnefeld FW, Barth J, Dick W, Doenicke A et al. (1994) Akuttherapie anaphylaktoider Reaktionen. Ergebnisse einer interdisziplinären Konsensuskonferenz. *Allegro J* 3: 211-224
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, et al. (1990) General considerations for skin tests procedures in the diagnosis of drug hypersensitivity. *Allergy Clin Immunol* 86: 325-332
- Aas K, Aberg N, Bachert C. European White Paper(1997) Aviso sprl, Van Moerbeke D. Bruxelles: 8-13
- Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, et al. (2013) Skin test concentrations for systemically administered drugs -- an ENDA/EAAACI Drug Allergy Interest Group position paper. *Allergy* 68: 702-712.
- Brown SG, Blackman KE, Hedde RJ (2004) Can serum mast cell tryptase help diagnose anaphylaxis? *Emerg Med Australas* 16: 120-124.
- Birbaum J, Porri F, Pradal M, Charpin D, Vervloet D (1994) Allergy during anaesthesia. *Clin Exp Allergy* 24: 915-921.
- Ledford DK (2011). Perioperative anaphylaxis:clinical manifestations, etiology and diagnosis. UpToDate.
- Benumof JL (1994) Difficult laryngoscopy: obtaining the best view. *Can J Anaesth* 41: 361-365.
- Cheney FW, Posner KL, Lee LA, Caplan RA, Domino KB (2006) Trends in anesthesia-related death and brain damage: A closed claims analysis. *Anesthesiology* 105: 1081-1086.
- Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, et al. (2005) Management of the difficult airway: a closed claims analysis. *Anesthesiology* 103: 33-39.
- Aberer W, Bircher A, Romano A, Blanca M, Campi P, et al. (2003) Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 58: 854-863.
- Mertes PM, Laxenaire MC, Malinovsky JM, Florvaag E, Moneret-Vautrin DA (2005) Skin sensitivity to rocuronium and vecuronium: prick-tests are not intradermal test. *Anesth Analg* 100: 1539.
- Assem E.S. Basel, Karger (1992) Allergic Reactions to Anaesthetics: Clinical and Basic Aspects. In: Moneret-Vautrin DA, Laxenaire MC (Eds) Skin tests in diagnosis to muscle relaxants and other anaesthetic drugs. (Edn) 145-155.
- Rodríguez-Bada JL, Montañez MI, Torres MJ, Mayorga C, Canto G, et al. (2006) Skin testing for immediate hypersensitivity to betalactams: comparison between two commercial kits. *Allergy* 61: 947-951.
- Nelson HS, Rosloniec DM, McCall LI, Iklé D (1993) Comparative performance of five commercial prick skin test devices. *J Allergy Clin Immunol* 92: 750-756.
- [No authors listed] (1990) The waiting period after allergen skin testing and immunotherapy. American Academy of Allergy and Immunology. *J Allergy Clin Immunol* 85: 526-527.
- McCann WA, Ownby DR (2002) The reproducibility of the allergy skin test scoring and interpretation by board-certified/board-eligible allergists. *Ann Allergy Asthma Immunol* 89: 368-371.
- Vanto T, Juntunen-Backman K, Kalimo K, Klemola T, Koivikko A, et al. (1999) The patch test, skin prick test, and serum milk-specific IgE as diagnostic tools in cow's milk allergy in infants. *Allergy* 54: 837-842.
- [No authors listed] (1993) Allergen skin testing. Board of Directors. American Academy of Allergy and Immunology. *J Allergy Clin Immunol* 92: 636-637.
- Pepys J, Bernstein IL (1985) The modified skin prick test. XII International Congress of Allergology and Clinical Immunology. Washington DC, United States