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Anaphylaxis During Perioperative Period in Pomeranian Region in Poland – 8 Year Survey.

KEYWORDS

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ABSTRACT *Background: Allergy in the perioperative period is a significant clinical problem.*

Methods: The author reports her own experience of a 8 - year survey conducted in Pomeranian region in Poland. Between January 2006 and December 2013, all patients who experienced perioperative anaphylaxis were referred to our allergy centre. They were selected out of 72 380 anaesthetized patients. Allergy was documented on the base of clinical history, skin tests, measurement of specific immunoglobulin E(sIgE) and serum mast cell tryptase (MCT).

Results: A total of 52 patients were studied (42 female, 10 male; age 39±7.75 years). Mild reactions, mostly cutaneous, were reported in 90.37% patients and severe potentially life-threatening reactions in 63.40% patients. An IgE-mediated mechanism was confirmed in 23 (of the whole amount of 52) patients. In our region the most etiological agents were opiates (6 cases), hypnotics and latex in 4 cases, antibiotics and neuromuscular blocking agents in 3 cases. These results should be taken into account while evaluating benefit-to-risk ratio of various anesthetic techniques in individuals.

Conclusions: It is important that a full explanation of what happened is given to patient, that the fact and results of any tests should be documented in the anaesthetic record, and that the patient is given a letter to warn future anaesthetists.

Introduction

Allergy in the perioperative period is an important clinical problem. Anaphylactic reactions to anaesthetic and associated agents used during the perioperative period have been reported with increasing frequency in most of the developed countries.

Anesthesiologists administer several drugs during surgery. Many of these drugs can elicit adverse drug reactions that fall apart into two major types. First, reactions that are usually dose-dependent and related to the pharmacological properties of the drug and/or metabolites. Second, reactions that are unrelated to the drugs pharmacological characteristics and that are less dose-dependent. These reactions comprise drug intolerance and drug-induced immune-mediated allergic and nonimmune-mediated so-called pseudo-allergic or anaphylactoid reactions. Clinical symptoms and reaction severity do not allow one to distinguish between an immune-mediated anaphylactic reaction and an anaphylactoid reaction resulting from direct non-specific histamine release[1]. Furthermore, no specific treatment has been shown to prevent the occurrence of anaphylactic reactions reliably [2,3,4,5].

Anaphylaxis, considered an acute type hypersensitivity reaction resulting primary from rapid antigen induction-usually IgE-depended release of potent mediators from mast cells and basophils-has been reported, although the term anaphylaxis should only be used for the most severe IgE-mediated, life-threatening, generalized or systemic hypersensitivity reaction [6,7]. Diagnosis of type I allergy, mediated by specific IgE antibody, is usually confirmed by skin tests, supported whenever possible by specific IgE assays [8,9,10,11,12,13].

The exact prevalence of anaphylaxis during anaesthesia is difficult to ascertain. The estimated overall frequency has been reported to vary between 1 in 3 500 and 1 in 13 000 procedures in French series and between 1 in 10 000 and 1 in 20 000 in an Australian study [14,15,16,17]. An IgE-mediated mechanism has been confirmed with 40% to 70% of cases. However, the reported prevalence varies considerably between different countries and controversy has arisen whether we are actually making the correct diagnosis, particularly with respect to allergy from NMBA and opioids [18,19,20]. In addition, in some series potential causes such as antiseptics have not been systematically studied [21,22,23].

Severe adverse reactions are infrequent during surgery, and IgE-mediated allergic reactions are the main contributors to morbidity and mortality in this kind of reaction during surgery [12]. Therefore, the anesthetists should ensure that patient is not re-exposed to the suspected causative substance. A warning should be written in the case notes and anaesthetic chart and the anaesthetist should inform patient and give him or her a temporary warning card.

In Poland, there have been few reports of allergic reactions during anesthesia [24]. To our knowledge, there are no epidemiological data available on the etiology of anaesthesia-related anaphylaxis in Poland. Therefore, the primary objective of this survey is to describe characteristics of patients that suffered from presumed anaesthesia-related anaphylaxis in the Pomeranian region in Poland that carried out a study following the same protocol coordinated by their allergy and anesthesiology teams.

In addition, this study provides the opportunity to briefly summarize on the potentials and shortcomings of the current diagnostic approach.

Materials and Methods

This was a 8 - year study, between January 2006 and De-

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cember 2013, of all patients who experienced an adverse reaction suspected of being allergic during anesthesia. The study was conducted in patients admitted to the Wards of Anaesthesiology in Szczecin and Poznan. The Ethics Committee of the Medical University of Szczecin approved the research. An anaphylactic reaction was the criterion for inclusion. All patients presented reactions in the operating room and/or recovery room. Patients referred from the Anaesthesiology Department to the Allergy Department for examination approximately 2 months after occurance of the reaction. The patient signed a written formal consent form before the controlled challenge test was performed. The diagnostic workup included the clinical history, standardized diagnostic protocol performed in an anesthesia outpatient clinic, skin tests to individual agents: patients were subjected for skin prick tests (SPT) and intradermal tests (IDT), serum-specific immunoassays and serum mast cell tryptase (MCT). Pathogenic mechanisms were defined in accordance with the new nomenclature of allergy proposed by the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organisation [6].

Recording of Medical History

Individual patient case histories were obtained from documentation given by referring anaesthetist, anaesthetic and surgical records and from patient's answers from the interview. If possible, full hospital case records of patients were reviewed, although for some patients referred from other hospitals and districts, these were unavailable. Clinical details and time course of events before, during and after treatment of the reaction and details regarding both the severity of the reaction and the response to therapy were noted.

The protocol included data on age, sex, prior allergies, date and time of reaction, clinical symptoms, reaction phase (induction/premedication, maintenance, recovery), number of previous anesthetic procedures, history of allergy (possible history of atopy or drug, food, or latex intolerance), chronic medications being taken during the procedure, anesthetic drugs given before the adverse reaction and management of the acute reaction were collected. Details were obtained regarding the degree of reaction, graded from I to IV, depending on increasing severity by Ring and Messmer (Table 1) [25,26].

Information about allergy investigations was recorded systematically: date of incident, type of skin tests performed (SPT and/or IDT), dilution of the tested drug leading to a positive reaction, cross-reactivity in cases of adverse reaction to a neuromuscular blocking agent (NMBA), results of histamine and MCT monitoring during the adverse reaction, and of IgE-specific assays testing responses to quaternary ammonium or latex when available.

Skin Tests

For the purposes of skin test determination, the author has made a protocol of skin prick tests. Skin test was performed by the trained allergy nurse. All patients underwent SPT and IDT with a battery of all drugs and/or substances administered during anesthesia suspected of being involved in the reaction and standardized SPT panel consisting of 10mg/ml histamine chloride, negative control (physiologic saline buffer solution) and positive (9% codeine phosphate) controls and SPT with latex (Fig.1). Prick tests with latex were performed using a standardized commercial fresh natural rubber latex extract. All solutions were prepared freshly prepared. Concentrations recommended by current guidelines were used at that time. [27]. They are shown in Table no 2. Skin tests involved two different steps: a SPT and, if this was negative, IDT using increasing concentrations of the drugs. Readings were taken after 15 minutes and assessed according to the criteria of the European Academy of Allergy and clinical Immunology (EAACI) [6]. A prick test result was considered positive when the diameter of the wheal was at least equal to half of that produced by the codeine test and at least 3mm greater than the negative control.

SPT's were performed on the anterior part of the forearm using a drop of undiluted drug, with the exception of atracurium (10mg/ml, Glaxo SmithKline,GB), mivacurium (10mg/5ml, Mivacron Glaxo SmithKline,GB), and morphine (10mg/ml, Morphini sulfas, Polfa, Poland), which were tested using a 1/10 dilution of the commercially available drug (Fig 2).

IDT were performed after the results of SPT had been obtained. They were performed either on the forearm or on the back by injection of 0.02-0.05 ml commercial drugs diluted in saline. Injections were performed every 15 minutes, according to a dilution scale, beginning with a 10-4 dilution when the prick test result was positive and a 10-3 dilution when the prick test result was negative. Injection dilutions were progressively increased to a 10-1 dilution as long as results remained negative. For morphine, rocuronium (10mg/ml, Rocuronium bromide, Organon Teknika, Eppelheim, Germany), and cisatracurium (5mg/ml, Nimbex, Glaxo SmithKline, GB), a maximal dilution of 10-2, and for atracurium(10mg/ml, Atracurium besilate, Glaxo SmithKline, GB) and mivacurium (10mg/5ml, Mivacron, Glaxo SmithKline, GB) a maximal dilution of 10-3 was used. Intradermal test results were considered positive when the diameter of the wheal was twice or more the diameter of the injection wheal. When the test result was positive, cross-reactivity to other NMBA's was investigated. Dermal reactivity to latex was assessed in all patients by prick test only, using a commercial reagent.

Specific IgE

Specific IgE toward latex, NMBA, suxamethonium (Chlorsuccillin, Pharma Swiss, Ceska Republika), morphine, and thiopental(Thiopental, Biochemie GmbH, Austria) were analyzed in serum samples using the Pharmacia uniCAP system (Cap- RAST, Pharmacia and Alastat, Diagnostic Product Corporation). Analysis was performed in serum samples collected both at the time of the reaction and at the follow-up examination. 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 interview details 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%.Values of allergen-specific IgE above 0.35kU/l were considered to be positive, except for the NMBA rocuronium and suxamethonium for which a drug-specific cut-off of 0.13 IU/L and 0.11 IU/L respectively was used. 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).

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Serum mast cell tryptase (MCT)
Two blood samples were taken by the anesthetist, the first within 2 hours after the reaction and the second after 2 months after reaction. Serum tryptase was measured using the Pharmacia UniCAP FEIA system (Pharmacia, Uppsala, Sweden). The MCT levels were considered increased if the 2-h MCT concentration was above 10µg/L (the upper reference area limit [97.5 %] of the laboratory). Analyses were repeated at follow-up to determine whether any patients had chronically increased background concentrations, because this could indicate systemic mastocytosis.

Statistical Analysis
Adescriptive statistical analysis (mean, median, percentage) was performed using SPSS Windows. P≤0.05 was considered statistically significant.

Results
During the study period, 72 380 surgical interventions were carried out under perioperative period. 52 (0.072 % ± 0.01%) patients suffered from perianesthetetic hypersensitivity reaction, suspected to be allergic. 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). A significant female predominance was observed [female, n=42 (80,76%); male, n=10 (19,23%), P<0.0001] with ages ranging from 20 to 79 years (mean 46 years). Nevertheless, this survey underestimates the real picture, because it has been demonstrated that in Poland 80% of patients presenting with anaphylactoid reactions during perioperative period did not have further allergic work-up. 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. In 42 of these a different NMBA was used. A history of previous general anesthesia was reported by 25 (of the whole amount of 52) patients (48%) and previous adverse reactions to nonanesthetic drugs was reported by 10 (19%) of patients. One patient had a history of one anaphylactic episode during general anesthesia. In two patients, careful assessment of the medical history revealed the onset of adverse reaction during a previous anaesthetic. In this cases, diagnosis of sensitization to NMBA and local anaesthetics had been made after the initial incident. Two patients were found to have systematic mastocytosis. Two patients died. The interview with the patient was supplemented by detailed clinical examination, including all systems, and basic laboratory tests (hematology, blood chemistry, 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. Atopy and the presence of drug or food intolerance were assessed by history. Immunological assessment by skin testing or immunoassay was performed systematically. The presence of atopy was reported in 7.5% of 52 patients. However, as reported previously, the presence of atopy was significantly more frequent in cases of latex allergy than in allergy to neuromuscular blocking agents (P<0.01). A history of drug allergy was present in 9.9% of 52 patients, a rate that approaches that reported in normal subjects (15%) [16].

All drugs and other antigens administered before the reactions are summarized in table 3. All allergic reactions were analyzed in relation to the phase when the reaction was induced and differences can be observed regarding the type of allergy and its etiology. With regard to the reaction phase, 39 reactions occurred during the induction phase, 10 during the maintenance phase, one during the recovery phase and two after premedication.

Clinical features
Table 4 shows the spectrum of clinical signs reported from the reactions. Mild reactions, mostly cutaneous were more frequent (90,37%) (Fig.3). Angio-oedema never occurred in isolation. Severe potentially life-threatening reactions were reported in 33 patients (63,40%). Most anaphylactic reactions were grade I° (67%) or grade II (17.30%); only 9.61% were grade III and 5.76% grade IV (table 5). No differences in symptom severity were observed with respect to sex, history of atopy, asthma or food and drug intolerance.

Diagnostc Tests
Plasma tryptase was determinated in 52 patients and high values were detected in nine (17.30%). 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. In six (11.53%) patients a sensitizing agent was confirmed (fresh frozen plasma, latex, augmentin (Amoxicillin, Glaxo SmithKline, GB) , meropenem (Meronem, Astra Zeneca), pethidin (50mg/ml, Pethidine hydrochloride, Polfa, Poland), thiopental, methohexital (Metohexital sodium, Eli Lilly, GB)). The tryptase level was normal in all patients tested with mild features and in three (5.76%) patients with severe anaphylaxis (grade III or IV), an IgE mediated cause for the reaction could be identified as well.Two patients (3.84%) had an elevated baseline tryptase (34,7 and 42,2µg/L) indicative for mastocytosis. One of them died of an 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 some extensive changes after ischemic stroke. The second patient was referred to the Clinic of Hematology for further diagnosis.

Specific IgE Assays
Methods for determination of specific IgE were calibrated using a standard IgE WHO 75/502 and results were expressed in quantitative units U/ml (kU/L), where 1 U corresponded to 2.44 mg IE. An analysis of results of specific IgE determination in 10 patients (19.23%) showed that the mean values were 2.57 ± 1.21 KU/L. Specific IgE toward suxamethonium was not detected in all patients. Specific IgE toward latex was positive in four (7.69%) cases, with an agreement of SPT of 97 %. Specific IgE against amoksiklav and morphine was detected in one patient (1.92%), against thiopental in two (3.84%) patients. In three (5.76%) patients presence of quaternary ammonium IgE was observed (atracrium, cisatracurium, rocuronium). In two (3.84%) patients, positive IgE assay results was not correlated with positive skin test results.

Sin-prick Testing
A positive reaction after allergen application occurred in the form of a wheal of three 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

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obtain an average wheal diameter.

In four patients (7.69%), positive SPT results showed clearly that latex was the causative factor of the reaction (Fig. 4 and 5). One of the patients (1.92%) was SPT positive to atracurium (Fig. 6), while the other subjects were SPT positive to augmentin and pethidine (Fig. 7). Positive SPT to NMBA (wheal size greater than 3 mm compared to the negative control) was observed in three patients (5.76%) (atracurium, cisatracurium, rocuronium).

Positive intradermal test results to NMBA occurred in 27 patients (51.92%). Increased dermographism caused that 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, noted in patient's records. Figures 6 and 7 show a diagram of skin tests performed to identify the causative agent of ADR in 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.

The results of SPT with propofol (10mg/ml, B.Braun Melsungen, Germany), suxamethonium, and fentanyl (50µg/2ml, Fentanylum, Polfa, Poland) were negative in all patients.

Severe dermographism making the skin-prick test difficult to interpret was seen in one patient. However, the presence of specific IgE toward rocuronium was indicated by a positive MCT result.

Cross-reactivity to NMBA

Cross-reactivity has a great clinical importance, because every NMBA is able to bridge specific IgE antibodies on the cell surface and produce anaphylactic reaction. Knowing the 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 three patients. The patients presented symptoms of anaphylaxis after the application of atracurium, cisatracurium and rocuronium. Only one patient who was positive to vecuronium (Norcuron, 1mg/ml, Organon Teknika, Holland), 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 (Pancuronium Bromide 2mg/ml, Organon Teknika, Germany), atracurium, cisatracurium and rocuronium. Intradermal tests were performed using increasingly diluted NMBA's to reveal the cross-sensitization of moderate severity. Positive SPT to succinylcholine was doubtful, while intradermal test results to succinylcholine were negative.

Diagnostic Conclusions

Patients were checked for their eligibility for planned anaesthesia before various surgical procedures basing on 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, being potentially responsible for the occurrence of ADR.

The NMBA's suspected of causing ADR included antibiotic in three cases, thiopental in four cases, latex was identified as the cause of hypersensitivity in four patients and opioids in six cases (Table 6). In contrast, only four 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.

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 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.

Discussion

This study represents one of the first epidemiologic surveys ever published of the incidence of anaphilaxis during anaesthesia over a 8-year period in Poland. Moreover, some patients who had experienced an adverse reaction during anaesthetic might have been investigated in centres different from those involved in this study. Our results confirm the large female predominance [female, n=42 (80,76%); male, n=10 (19,23%)] of anaphylactic reactions, although it is less marked than that reported in other studies, where it ranges from eight females/one male [16,28,29].

Correct management of anaesthesia-related anaphylaxis requires a multidisciplinary approach with prompt recognition and treatment of the acute event and identification of the offending agents and strict secondary prevention with absolute avoidance of the implicated compounds.

The diagnosis of anaphylactic reactions in the study was determined basing 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. The interview was a source of key information about the symptoms of hypersensitivity, which might correspond with 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 patient's condition, make the treatment difficult and can be life-threatening in extreme situations [30,31,32]. 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% ± 0.002.

Comparison of these figures with the ADR values presented by the author basing on her own observations, conclude that from the epidemiological point of view, the events are comparable and weight of the ADR issue in the perioperative period should be emphasized. Our findings indicate the validity of the use of skin testing in patients anaesthetized for surgery and in the perioperative period. Until recently times, it was believed that the combined use of IDR with SPT and specific IgE would eliminate the need

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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 [33,34,35]. 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.

Serum tryptase is an indirect measure of mast cell degranulation and can be useful to distinguish mast cell dependent reactions from other causes of perioperative cardiovascular instability such as cardiogenic shock. Tryptase concentrations peak between 30 and 60 min; thus, its concentration should be determined approximately within an hour after reaction has started. Increased tryptase concentrations in postmortem sera suggest systemic anaphylaxis as a cause of death. However, a negative test result does not completely rule out anaphylaxis, particularly if sampling is performed at the beginning of the reaction, or in cases of mild reactions [16,31]. This is confirmed by the specificity of tryptase measurement in the diagnosis of anaphylaxis (with an elevated level in17.30%) observed in our series. The diagnosis of anaphylaxis should not rely on a single test, and patients in whom MCT concentrations are not increased still require skin testing.

Generally, reactions were predominant in the induction and recovery phases and manifested mainly as cutaneous symptoms. Reactions to drugs coincide with the phases when they were administered.

In most cases clinical reactions were grade I and II (84.30% of cases) and life-threatening (15.37% were grade III or IV).

Identifying the correct causative substance is also difficult, because during anaesthesia and operation, patients are often exposed to a large number of potential allergens in a very short time. Correct identification of the causative substance in a suspected allergic reactions during anaesthesia is obviously very difficult as 92.30% of suggestions were not confirmed in subsequent testing at the allergologist and only 13 out of 52 patients (25%) were completely correct. This may suggest that the smaller the number of potential allergens is, the greater is the chance of a correct identification.

Diagnosing an allergic reaction and distinguishing it from other symptoms occurring during anaesthesia is difficult, while 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.

Differences regarding the etiological agents were found. In most studies, NMBA are most frequently followed by latex [16,17,18,19]. However, in present study opioids caused most of allergic reactions followed by hypnotics, latex and NMBA's. This current study shows the relatively low frequency of NMBA reactivity and a lower proportion of NMBA allergy relative to other drug allergies. Cross reactivity between NMBA is relatively uncommon, being identified in only one patient in this study. Most patients with NMBA reactivity were not sensitized to all NMBA. This difference could be explained by referral bias, differences in allergy testing methods or actual geographical differences in sensitization toward the relevant antigens.

Opiates are known to cause both IgE mediated and non-IgE mediated degranulation of mast cells and may thus produce both anaphylactic and anaphylactoid reactions. Six patents were diagnosed as having reactivity to opiates. Six patients demonstrated a positive skin reaction at a dilution of 1:1000, consistent with an IgE mediated reactivity to the implicated opiate. In one patient, hypotension and urticaria occurred during anaesthesia when pethidine was used and further episode of urticaria and hypotension occurred during pethidine infusion in the postoperative phase. The reaction terminated when the infusion was ceased.

Hipersensivity to hypnotics was found in four patients. One of them had severe reaction IV° with cardiac arrest and death.

Latex caused allergic reactions in four cases. In 2003, Dybendal et al reported one out of 18 cases induced by latex [3]. Reactions to latex were most severe than those observed with neuromuscular blocking drugs ($P<0.0001$). Despite screening of patients by specific questioning in the pre-anaesthetic questionnaire in most hospitals in our region, including questioning around sesitisation to specific foods, four patients had unidentified reactivity to latex. One of the patients, who had severe reaction (grade III°) gave a history of previous surgical procedures. It is important to correctly identify the condition and to screen for any associated risk factors to avoid the risk of subsequent reactions.

Antibiotics caused allergic reactions in three cases. Betalactam antibiotics involved allergic reaction in two cases, carbapenem (Meropenem) reported in one patient. Two of them had severe reaction and one death. Penicillin and other betalactams are also considered to be emerging antigens, and antibiotic therapy occupies the third cause of anaphylaxis and moreover, could increase [36,37,38,39, 40, 41]. NMBA's sensitization was involved in three cases (only 0.004%) (atracurium, rocuronium and cisatracurium). Reactions to neuromuscular blocking drugs appeared to be less severe than reactions to latex. A correction factor based on the average number of vials used during anaesthesia in one patient, defined with and accepted by the principal manufacturers of neuromuscular blocking agents (Glaxo Wellcome and Organon Teknika) was also used to estimate the number of anaesthetized patients exposed to each compound. A significant difference was observed when percentage of anaphylactic reactions to each drug was compared with the estimated percentage of patients, who received these drugs over the same time period ($P<0.0001$).

Coloids sensitization was involved in two cases (Gelatin solutions) [42]. Anaphylaxis due to sensitivity to gelofusine and other plasma expanders is well described, usually causing reactions during resuscitation or anaesthesia with estimated incidence of 0.04-0.15 % [43,44,46].

Our study results also reveals that 5% of the patients demonstrate double or multiple sensitizations.

In our study, positive diagnosis was mainly based on clinical history and skin test results, often corroborated by specific IgE assay. A recent study also questioned the specificity for SPTs with NMBA's [40, 44, 45,46].

In summary, anaesthetists should always think of an anaphylactic reaction with unexpected, sudden or severe hypotension. A high index of suspicion and early, aggressive therapy with adrenaline by intravenous injection is vital. An adrenaline

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infusion should be instituted as soon as possible, with titration against the heart rate and blood pressure.

Reports of allergic reactions during anaesthesia done in Poland may be of a questionable value, if basing only on observations and guesses made in emergency situations.

Finally, it is significant that a full explanation of what happened is given to the patient, that the event and the results of any tests should be documented in the anaesthetic record, and that the patient is given a letter to warm future anaesthetists. A permanent warning bracelet should be worn by the patient.

Table 1. Classification of clinical manifestations of anaphylaxis during anesthesia. Based on Ring and Messmer [26]

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

Drug name	Drug concentration (mg/ml)	Skin prick testing	Intradermal testing			
		Dilution	Dilution			
Atracurium	10	1:10	1:10,000	1:1,000	X	X
Cis-atracurium	2	1:1	1:10,000	1:1,000	1:100	X
Mivacurium	2	1:10	1:10,000	1:1,000	X	X
Pancuronium	2	1:1	1:10,000	1:1,000	1:100	1 :10
Rocuronium	10	1:1	1:10,000	1:1,000	1:100	X
Suxamethonium	50	1:5	1:10,000	1:1,000	1:500	X
Vecuronium	4	1:1	1:10,000	1:1,000	1:100	1 :10
Etomidate	2	1:1	1:10,000	1: 1,000	1:100	1: 10
Midazolam	5	1:1	1:10,000	1:1,000	1:100	1: 10
Propofol	10	1:1	1:10,000	1:1,000	1:100	1 :10
Thiopental	25	1:1	1:10,000	1:1,000	1:100	1 :10
Other e.g., Morphine	10	1:10	1:10,000	X	X	X

Table 3. Drugs administered before the reaction

Drugs administered during procedure	Number of administrations in cases with ADR
NMBA (n=40)	
Succinylocholine (Suxamethonium)	19
Vecuronium bromide (Norcuronium)	10
Rocuronium bromide (Esmeron)	1
Atracurium besilate (Tracrium)	1
Cisatracurium (Nimbex)	27
Latex (n=52)	52
Antibiotics (n= 9)	
Penicillin	5
Cephalosporin	3
Meropenem	1
Hypnotics (n= 51)	
Thiopental	33
Propofol	11
Etomidate	4
Ketamine	2
Sedativa (n=24)	
Midazolam	32
Diazepam	10
Opioids (n= 51)	
Morphine	8
Fentanyl	34
Sufentanyl	3
Pethidine	7
Colloids (n=3)	
Gelatine (Gelafundin)	2
Haestarch (HES)	9
Dextran	3
NSAIDs (n=3)	
Diclofenac	2
Ketoprofen	2
Paracetamol	2
Other (n=47)	
Aprotynin	4
Atropine	3
Fraxiparine	40
Local anaestetics (n=6)	
Bupivacaine	3
Lidocaine	3

n = number of patients

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Table 4. Reported clinical signs of anaphylaxis (n=52)

Clinical signs	Number of cases
Skin symptoms	47 (90,37%)
Angioedema + Cutaneous symptoms (flushing, urticaria, erythema)	5 (9,61%)
Respiratory symptoms	1 (1,92%)
Bronchospasm, ventolatory impairment, Oedema pulmonis	10 (19,23%)
desaturatio, cyanosis	17 (30,76%)
Cardiovascular symptoms	2
Arterial hypotension	(3,84%)
Cardiac arrythmias (Bradycardia/tachycardia)	2/10 (3,84/19,23%)
Cardiac arrest	3
Death	(5,76)
	2 (3,84%)

Table 5. Grading of reactions according to severity related to whether a suggestion of causative allergen was made. Grade I, mild self limiting reactions(isolated skin symptoms), grade II, moderate reactions quickly responding to therapy(hypotension or bronchospasm), grade III, severe reactions requiring prolonged treatment(anaphylactic shock), grade IV (cardiac arrest).

Grades	Number of cases n %
0°/I°	35 67.30%
II°	9 17.30%
III°	5 9.61%
IV°	3 5.76%

Table 6.Triggering factors of ADR confirmed with complete allergologic tests

Opiates 6
Hypnotics 4
Latex 4
Antibiotics 3
NMBA-s 3
Colloids, plasma/blood 3
Summary 23/52

FIGURE LEGENDS

Fig.1. Standard panel of drugs

Fig.2. Skin tests used to identify an agent causing anaphylaxis during anaesthesia

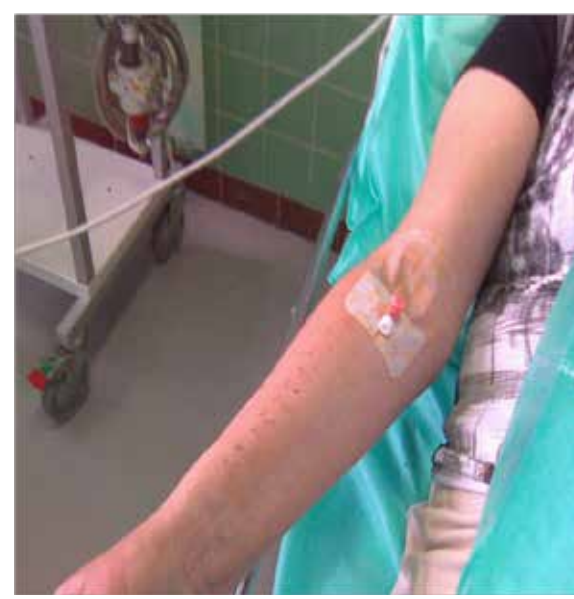

Fig.3. Skin alternations – hives (urticaria) on the chest.

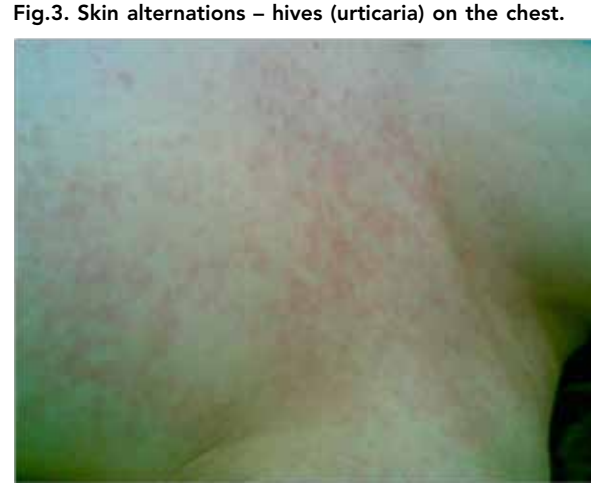

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Fig.4. Positive SPT to latex

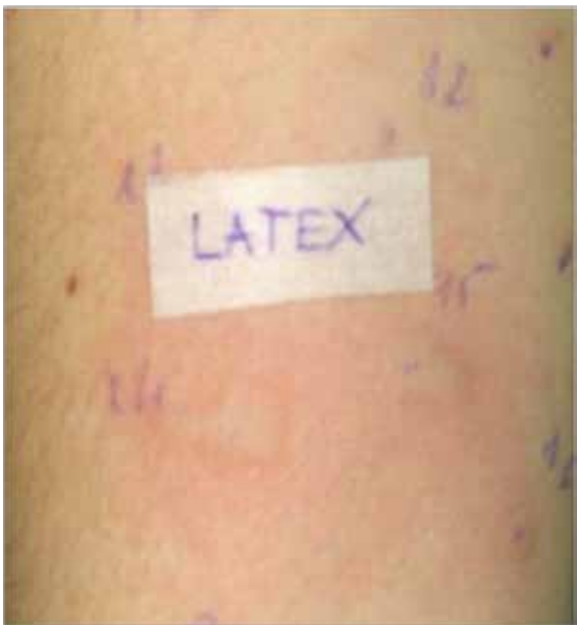


Fig. 5 Positive SPT to latex

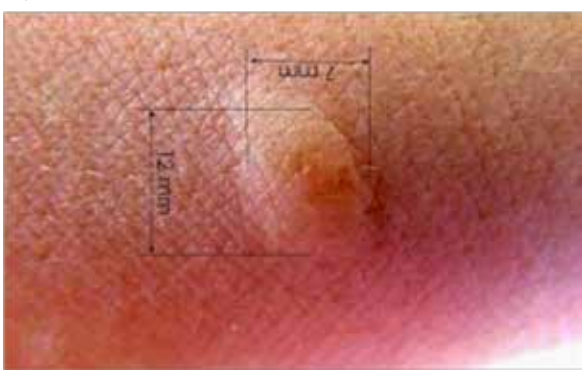


Fig.6. Positive SPT to atracurium

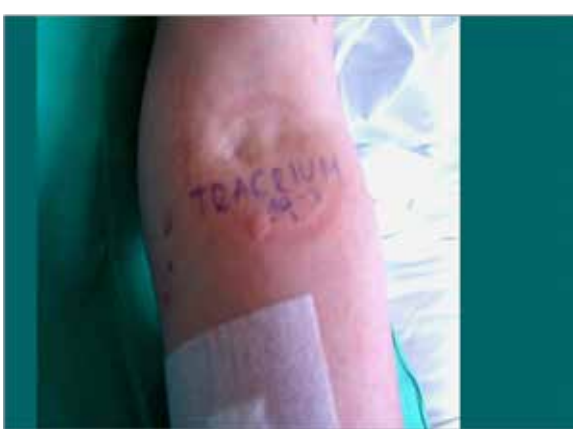
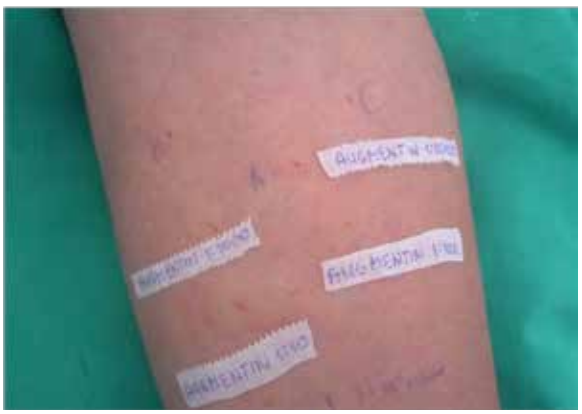


Fig.7. Positive SPT to augmentin



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