The prevalence of allergic reactions in general population shows a constant rise. It has been estimated that up to 40% of surgical patients have a positive history of some kind of allergy. These patients represent a challenge during perioperative evaluation, since they can be exposed to a large variety of drugs and substances during surgery and anesthesia. A lot of adverse drug reactions show similar clinical presentation with allergic reactions. The latter are usually poorly explored since preoperative allergology testing is performed in a limited number of patients. Management of patients with history of allergy is impeded by the fact that most of allergens cross-react in a manner that is not always easy to predict. Allergies can manifest themselves with a broad spectrum of clinical symptoms, ranging from mild skin symptoms such as itch and urticaria, to a life-threatening anaphylactic reactions followed by hypotension, bronchospasm and cardiovascular collapse. Prevention of allergic reactions during perioperative period requires detailed history taking in order to identify patients at risk, optimization of anesthesia strategy, pharmacological premedication and further allergology diagnostic work-up in selected cases.

Key words: allergy, perioperative management, anesthesia, surgery

INTRODUCTION

Perioperative period represents a specific setting because a patient is exposed to a variety of drugs and substances over a short period of time. Many of these drugs can cause adverse reactions that can be divided into two major types.

First type of reactions are usually dose-dependent and induced by pharmacological characteristics of the drug, while the second type is unrelated to drug properties and is rarely dose-dependent.  
This group of adverse reactions can further be divided into: drug intolerance, idiosyncratic reactions and drug induced immune-mediated (allergic) and nonimmune-mediated (anaphylactoid) reactions. Since anaphylactic and anaphylactoid reactions share the same clinical presentation, it is proposed by the European Academy of Allergy and Immunology that anaphylactic-type reactions should be classified according to the underlying mechanism into allergic anaphylaxis (further subdivided in IgE-mediated and non-IgE-mediated) and nonallergic anaphylaxis.

PATHOPHYSIOLOGY OF ALLERGIC REACTIONS

The fundamental role of immune system is to protect against infections, but sometimes immune system itself can cause tissue damage or disease. Those pathological immune reactions are called hypersensitivity. According to revised, broader definition, hypersensitivity is reaction initiated by exposure to a particular stimulus at a dose tolerated by normal subjects.

Allergy represents a hypersensitivity reaction caused by immunological mechanisms. In other words, the immune response to foreign antigens in allergy can be either disturbed or uncontrolled, leading to tissue damage. It is mediated by endogenous mediators, such as histamine, bradykinine, proteases, metabolites of arachidonic acid, or by complement activation.

It should be emphasized that allergy can be both antibody- and cell-mediated. Although the most important antibody responsible for allergic reaction belongs to IgE isotype, there are plenty examples of allergic reactions mediated by IgG antibody (as in allergy to immune complexes containing dextran-type III reaction), or IgA and IgM antibodies (as in some kinds of food allergies). Finally, contact dermatitis is an example of cell-mediated allergy conducted by sensitized lymphocytes. The most common type of allergic reaction is initiated by an interaction of allergen with specific IgE antibodies present on mast cells.
and basophils of sensitized persons. Specific binding of allergen to IgE activates those cells and triggers mediator release, which than produce biologic actions such as vasodilatation, increased capillary permeability, changes in inotropy, smooth muscle contraction and bronchial and gut mucus production. Secreted cytokines induce local inflammation by stimulation of leukocyte mobilisation. Eosinophils are the key component of majority of allergic reactions, being the important cause of tissue damage.

CLINICAL PRESENTATION OF ALLERGIES

Clinical presentation of allergic reactions vary considerably, which can be attributed to differences in the amount of mediators released from mastocytes as well as to the different sites of allergen-IgE reaction.

There are many well-defined allergic diseases, such as allergic rhinitis and sinusitis, conjunctivitis, asthma, skin diseases (contact or atopic dermatitis), various food allergies, etc. The most severe form of hypersensitivity is anaphylaxis, representing severe, life-threatening and generalised reaction induced by allergic and nonallergic mechanisms. In allergic anaphylaxis, patient is already sensitized to a specified allergen, with antibodies or specific lymphocytes formed after previous exposure. Non-allergic anaphylaxis results from a direct effect of allergen on mastocytes and basophils. Independently of the underlying mechanism, clinical picture of anaphylaxis usually occurs within 5-10 minutes of the exposure to the antigen.

Initial symptoms are rather local (itching, sneezing, erythema) and they progress to a generalized reaction with possible angioedema, bronchospasm, hypotension and cardiovascular collapse. Severity of anaphylaxis can vary, but it should be noted that presence of hypotension and bronchospasm is not necessary for its diagnosis.

FOLLOW-UP OF ANAPHYLAXIS AND ALLERGIES

The diagnosis of anaphylaxis can be made on the basis of its clinical presentation which can be dramatic and related to the exposure to a suspected antigen. Anyway, a lot of symptoms of anaphylaxis are nonspecific and syndrome can mimic the other entities such as pulmonary embolism, myocardial infarction, vasovagal reaction, etc.

Specific tests to differentiate anaphylaxis from the above mentioned conditions can be divided into primary and secondary investigations.

Primary tests are performed soon after the occurrence of anaphylactic reaction. Blood samples are obtained in the first 1-4 hours after the reaction and are used to determine the value of serum tryptase. Tryptase is a neutral protease found almost only in mast cells, and its elevated level represents a marker of mast cell activation. Its concentration is in correlation with the severity of anaphylaxis, and the values turn to baseline value after 24 hours in most cases, with elimination half-life of 2.5h. Primary investigation can also determine the cause of anaphylaxis measuring the IgE antibody in serum by radioallergosorbent or fluorimunoassay. Those tests are antigen specific, but available for a limited number of antigens and should be performed within six months after anaphylaxis.

Secondary investigations in allergy assessment consist of skin tests, in vitro testing and sometimes of drug provocative tests.

Skin tests are preferred investigation in most countries, performed in the form of skin prick and intradermal tests, where skin mastocytes are exposed to a suspected diluted or undiluted allergen. IgE-mediated reaction occurring in the skin of sensitized patients accompanied with histamine release, can be visualised in the form of wheal and flare response. Those tests should be conducted in specialised institutions only and after all medications that could interfere with test results have been stopped (corticosteroids, antihistamines...). The optimal time for performing skin tests is at least six weeks after anaphylaxis in order to avoid false negative results arising from temporary depletion of specific IgE antibodies or nonresponsiveness of the effector cells.

EPIDEMIOLOGY

The incidence of all kinds of allergic reactions has been steadily rising in the past decades, parallely with growing exposure to numerous chemical substances in human environment. Taking a history of drug allergy is the inevitable part of every medical admission and that information influences further drug prescription and sometimes the global therapeutic approach.
There are several studies regarding the incidence of self-reported drug allergies. Depending on study population, definition of drug allergy and other factors, the reported incidence has been between 7.8% (in general population) and 39% (in surgical population). Unfortunately, the proportion of patients who underwent further investigation following the adverse reaction is less than 30-50% and it has been shown that between 40-50% of them are confirmed as being allergic. Patients with self-reported allergies most commonly considered themselves allergic to antibiotics (more than 40% to penicillins and other β-lactams), NSAIDs, opioids, iodine, diuretics, etc. Allergic reactions in the perioperative period, on the other hand, most commonly involved neuromuscular blocking agents (58.2%), latex (16.7%) and antibiotics (15.1%), with other substances being far less frequent.

The most frequently reported symptoms and signs of allergic reactions are skin rash and urticaria (47-73%), generalised itch (30-48%), angioedema (up to 40%), dyspnea, wheezing and bronchospasm (7-29%), nausea and difficulty to swallow, hypotension (6-15%) and loss of consciousness (8.5%). Drug allergies occurring in the perioperative period are of major concern to anesthesiologists and all medical stuff involved in perioperative management. Although drug anaphylaxis during surgery is rare with the incidence ranging from 1/13000 surgical procedures (under general, regional and local anesthesia) to 1/6500 general anesthetics with use of muscle relaxants, they are very important as they can be responsible for up to 4.3% of deaths occurring during general anesthesia with an additional 2% of survivors with significant residual brain damage.

**AETIOLOGY OF ALLERGIC REACTIONS DURING THE PERIOPERATIVE PERIOD**

**Neuromuscular blocking agents (N MBA)**

NMBA are responsible for up to 60% of allergic reactions during general anesthesia. This heterogenous group of drugs can induce two types of drug reactions. First one is caused by an immunological mechanism involving IgE mediated reaction with the quarternary ammonium (NH₄⁺) as main antigenic epitope. The second one involves nonimmunological stimulation of mast cells with consequent histamine release. This anaphylactoid reaction is commonly seen with benzyloquinolinium-type NMBA such as atracurium, mivacurium and d-tubo-curarine. Increased prevalence of rocuronium anaphylaxis has also been registered lately.

Cross-reactivity between NMBA is common due to ubiquitous ammonium group present in those drugs, and its prevalence is estimated to be about 75% by skin tests and up to 100% by radioimmunoassay tests. A lot of over-the-counter drugs and cosmetics are capable of sensitizing

<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk factor</th>
<th>Risk - related agents</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Allergy to cosmetics</td>
<td>NMBAs</td>
<td>Avoid histamine liberating substances, Follow advice from allergological investigation (if present). Use inhalation agents, Use as few drugs as possible. Use local/regional techniques or avoid NMBAs. Inject drugs separately and slowly. Consider premedication with antihistamines (anti H1 plus H2 agents) and corticosteroids for at least two days</td>
</tr>
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<td></td>
<td>Family history of GA anaphylaxis</td>
<td>All agents</td>
<td></td>
</tr>
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<td></td>
<td>Previous exposure to GA</td>
<td>NMBAs</td>
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<tr>
<td>Moderate</td>
<td>Asthma, allergy, Atopy, Penicillin allergy</td>
<td>All agents, Cephalosporin</td>
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<td>Allergy to eggs/soybean oil</td>
<td>Propofol</td>
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<td>High</td>
<td>Multiple drug allergies</td>
<td>All agents</td>
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<td>Previous anaphylaxis during GA</td>
<td>All agents, Latex</td>
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<td>Sensitization to exotic fruits</td>
<td>Cephalosporin</td>
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<td>Seafood allergy</td>
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<td>Spina bifida</td>
<td>Latex</td>
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**Abbreviations:** N MBA-neuromuscular blocking agents, GA-general anesthesia
person to NMBA, which can be explained by the presence of ammonium groups in their molecules. It is not unusual that, because of cross-reactivity, a person is allergic to all NMBA. It is therefore the optimal approach to avoid relaxants in those patients in the future whenever possible. It’s interesting that individuals can remain sensitized for a long period of time (up to 30 years) after developing antibodies toward NMBA.

Natural rubber latex

Natural rubber latex is a complex mixture of lipids, polylisoprene, phospholipids and proteins. The protein component of latex is responsible for the majority of allergic reactions to latex, and over 240 potentially allergenic proteins have been identified in the final latex product.

The first mention of allergic reaction to rubber gloves appeared in literature in 1933. The incidence of allergy to latex has increased sharply in the past few decades.

There are three distinct types of reactions that can be seen in persons exposed to latex containing products: irritant dermatitis, type IV and type I hypersensitivity. First two types of reactions are caused by chemical additives used in manufacturing, while the latter is induced by proteins found in latex.

It is important to identify the at-risk individuals for perioperative anaphylaxis who can be divided into genetically predisposed (atopic) and those patients with high level of exposure to latex (patients with multiple surgical procedures, health care personnel, people with occupational exposure to latex).

Cross-reactivity with numerous plant proteins similar to those found in latex has been observed, which led to description of "latex-fruit syndrome". Persons allergic to tropical fruits (kiwi, banana, avocado) and chestnuts might be allergic to latex as well. The prevalence of latex allergy in general population is much smaller ranging from <1% to 6.7%.

Antibiotics

All types of antibiotics can potentially cause allergic reactions and anaphylaxis. Penicillins and other β-lactams account for up to 70% of antibiotic-induced anaphylactic reactions in perioperative period. Penicillin allergy is also the most frequently self-reported allergy in surgical patients, although true allergy to penicillin is estimated at approximately 0.01%. It is known that penicillins cross-react with cephalosporins, amidopenicillins and carbapenems, which frequently guides clinicians in prescribing non-β-lactam antibiotic to patients with history of allergy to penicillin. However, the risk of cross-reaction and anaphylaxis has been probably overestimated and cephalosporins can be taken into account in penicillin-allergic patients. Vankomycin can express two types of hypersensitivity reactions: "Red man syndrome" which results from nonspecific mediator release, and immunological IgE-mediated anaphylaxis which is extremely rare. Quinolones are the third most important group of antibiotics causing peri-operative anaphylaxis. It should be mentioned that locally applied antibiotics such as bacitracin and some antimycotics can also lead to potentially life-threatening allergic reactions.

Anesthesia induction agents

Allergic reactions and anaphylaxis after thiopental use are rare, happening approximately in 1/25000 administrations, with previous exposure and female gender being recognized as risk factors.

Propofol is responsible for rare allergic reactions on induction, but it can induce direct histamine release from mast cells. Although one case report describes anaphylactic reaction after propofol use in a child with multiple food allergies (including an egg and peanut), the cross-reactivity hasn’t been proved. Despite the fact that the product literature cites soy oil allergy as the contraindication for propofol use, an allergic reaction in soy allergic people has never been documented after propofol use. It is probably because the soy oil in propofol is refined, thus containing a very small amount of allergenic particles.

Other induction agents (ketamine, benzodiazepines, etomidate) are extremely rarely a cause of allergic reaction.

Local anesthetics

Local anesthetics (LA) are not frequently triggers of allergic reactions, although reported incidence of suspected allergy toward LA in various studies is up to 30%. It must be said that the vast majority of adverse reactions after LA administration do not have immunological background and it is estimated that only 1% of them are being allergic. Most of reactions such as tachycardia, palpitation, light-headedness, syncope or hypotension are the consequence of overdosage or inadvertent intravascular injection of LA, or represent the effect of vasoconstricting agents. True allergies toward LA are more commonly seen with ester-type local anesthetics since they are metabolized to highly antigenic para-aminobenzoic acid. Cross-reactivity between amide- and ester-type LA are extremely rare.

Aspirin and NSAIDs

The prevalence of NSAID reactions in general population is not greater than 1%. It is, however, known that most of these reactions are non-immunologically mediated through inhibition of cyclooxygenase (COX) with subsequent depletion of prostaglandin E2 and release of mediators from mast cells and eosinophils. Diagnosis of aspirin and NSAID hypersensitivity reactions can be obtained by drug provocation tests.

Protamine

Protamine is a low weight protein extracted from fish sperm, which forms a stable salt in the presence of heparin, resulting in loss of its anticoagulant activity. It is known to elicit direct histamine release, leading to severe and sometimes fatal hypotension and bronchospasm. Its
use is also associated with pulmonary hypotension resulting from complement activation and thromboxane release.

Patients at risk for anaphylaxis to protamine are those allergic to seafood, men after vasectomy (because of developing circulating antibodies toward spermatozoa) and those patients previously exposed to protamine (eg. diabetic patients using protamine-containing insulins-NPH).30

Protamine allergy is of major concern during the perioperative period, since there is no alternative drug for reversal of heparine anticoagulant action.

**Plasma volume expanders (colloids)**

Synthetic colloid solutions are capable of producing anaphylactic reactions ranging from rush and urticaria to severe hypotension and bronchospasm. Generally, low molecular dextrans cannot induce antibody formation, but may cross-react with antibodies formed in response to polysaccharides of bacterial origin. Hydroxyethyl starch (HES) has been identified as a causative agent of allergy in 0.006% exposures. Anaphylaxis from albumin is anecdotai.31

**Radiocontrast media**

Reactions to contrast media are more frequent with ionic than nonionic agents, but its potential for causing anaphylaxis is largely dependent on iodine concentration.32 The incidence of anaphylaxis after exposure to iodine contrasts is at least 0.7%, while the reactions involving non-specific toxic mechanism are much more common. Identified risk factors for anaphylaxis upon administration of a contrast medium are anxiety, age, female gender, intravenous injection route, history of allergy, mastocytosis and previous reaction to a contrast medium.

**Antiseptics**

Patients frequently report allergies to disinfectants and antiseptics. There is plenty of evidence that chlorhexidine salts can induce contact dermatitis, urticaria and even anaphylaxis. The incidence of reactions arising from skin disinfection is probably underestimated, as it has been shown by study of Kroigaard et al, where chlorhexidine accounted for 27% of overlooked perioperative allergic reactions.33 Allergies to povidone-iodine are very rare and they are presented in literature usually as case reports.34

**PERIOPERATIVE MANAGEMENT OF PATIENTS WITH PREVIOUS ALLERGIC REACTIONS**

Ideally, all patients who suffered anaphylactic reactions, specially during previous anesthesia, should undergo thorough allergo-anesthetic investigation. Unfortunately, this is not the case in real world, and many patients presenting for elective or urgent surgery and diagnostic procedures claim to be allergic without any information an further follow up after the allergic reaction.

In order to prevent anaphylaxis during perioperative period, it is neccessary to identify patients at risk. Detailed history taking (if no allergology records are available) helps in differentiating true allergic from other adverse drug reactions. Risk evaluation, however, should never lead to postponing of urgent surgery or surgery scheduled for malignancy. It should be noticed that patients with asthma and the atopic constitution are at increased risk for allergic reactions to all agents that can be administered during anesthesia.

If patient reports allergy to a specific agent or the allergy has been documented by a previous diagnostic test, that agent should be avoided or replaced with alternative.

If the allergic reaction occurred during a previous general anesthesia (with no further follow-up), local anesthesia should be considered, as a true allergy to LA is extremely rare. In a case where general anesthesia is inevitable, it should be conducted with volatile agents. When there is no diagnostic test to confirm or reject the allergy to NMBA, it is prudent to use regional blocks or volatile agents if those techniques are suitable. Latex-free environment should be provided for patients with risk for latex allergy and alternative drugs should be given to those patients reporting allergies to antibiotics and NSAIDs. Prophylactic treatment can be considered for patients at risk, but it should be emphasized that there is no treatment with efficacy in all clinical situations. Although premedication with antihistamines and corticosteroids cannot prevent anaphylactic shock, it has been shown that the associated use of H1- and H2-antagonists is able to prevent or reduce bronchospasm and hemodynamic irregularity due to non-specific histamine release.

**Suggested premedication in non-emergency cases**

In patients with low or medium risk, premedication with combined intake of anti-H1 and anti-H2 agents and corticosteroids is suggested for at least two days and last tablet taken 1 hour before anesthesia or infusion of iodinated contrast. High risk patients should be premedicated with higher dosages of anti H1 and anti-H2 and corticosteroids over a longer period of time (3-4 days before surgery). An additional dosage (40 mg methylprednisolone) may be given on hour prior to anesthesia. All patients with bronchial obstruction or asthma should be pretreated with inhaled agents

**Premedication in emergency cases**

Those cases require rapid parenteral premedication with antihistamines and corticosteroids just before the start of anesthesia. Anesthetic approach to patients with history of allergies is summarized in table 2.

Patients with previous reaction to contrast medium who require re-exposure, should be given a low-omulsarity contrast, as the reported incidence of anaphylaxis with such agents is lower.35

Radiology offices where contrast media are usually applied, should be equipped with resuscitation drugs and devices, and patients must be observed for at least 20-30 minutes after the injection of contrast medium in order to notice early signs of delayed reaction.
Finally, each reaction occurring after drug or contrast administration in the perioperative period should be entered into patient’s personal medical chart and any suspected anaphylactic reaction should be investigated using a variety of intra- and postoperative diagnostic tests with multidisciplinary approach.

CONCLUSION

Increasing consumption of drugs and exposition to various chemicals resulted in a fact that more surgical patients report to be allergic or suffer from an allergic disease. Allergies remain to be of major concern to whole medical team involved in perioperative management. There is an increasing need for better understanding of pathophysiology of all reactions induced by anesthetics and substances used during the perioperative period. In order to prevent potentially fatal consequences and offer their patients an optimal protection, all physicians operating in the absence of an allergy consultant, should stick to the literature based guidelines.

SUMMARY

PREOPERATIVNA EVALUACIJA BOLESNIKA SA ALERGIJOM

Učestalost alergija u opštoj populaciji je u konstantnom porastu. Procenjuje se da čak do 40% hirurških bolesnika navodi anamnestički podatak o nekoj vrsti alergije.

Takvi bolesnici predstavljaju poseban izazov u preoperativnoj pripremi, budući da su u neposrednom perioperativnom periodu izloženi velikom broju različitih lekova i supstanci. Mnoge neželjene reakcije na lekove mogu ispoljiti kliničku sličnost sa alergijskim reakcijama, a preoperativna alergološka ispitivanja se provode kod malog broja bolesnika. Pristup bolesnicima sa alergijom dodatno otežava činjenica da mnogi alergeni pokazuju ukrštenu reaktivnost koju je nekada teško predvideti.

Alergije imaju veoma širok spektar kliničkog ispoljavanja, od blagih kojih simptoma, poput svarba i utikarije, do životno ugrozavajućih anafilaktičkih reakcija praćenih hipotenzijom, bronhospazmom i kardiovaskularnim kolapsom. U cilju prevencije alergijskih reakcija, neophodno je sprovesti detaljno anamnestičko ispitivanje kako bi se identifikovali bolesnici sa povećanjim rizikom i pažljivo planirati strategiju prevencije ove komplikacije.

U nekim slučajevima je potrebno razmotriti i dodatna alergološka testiranja i preoperativnu pripremu antihistaminicima i glukokortikoidima.

Ključne reči: alergija, perioperativni tretman, anestezija, hirurgija

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