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Nonallergic Hypersensitivity to Nonsteroidal Antiinflammatory Drugs, Angiotensin-Converting Enzyme Inhibitors, Radiocontrast Media, Local Anesthetics, Volume Substitutes and Medications used in General Anesthesia

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SUMMARY Urticaria and angioedema are common allergic manifestations and medications are one of common triggering factors. The most severe immediate drug reaction is anaphylaxis. Apart from the well established IgE-mediated immediate type hypersensitivity reactions, the pathogenesis of drug-induced urticaria, angioedema and anaphylaxis often remains obscure. In this article, emphasis is put on nonallergic reactions to the most commonly used drug groups of nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, radiocontrast media, volume expanders and drugs used in general anesthesia. Urticaria is the second most common drug eruption after maculopapular exanthema. The mechanisms of acute urticarial reactions are multiple, mostly IgE mediated, but some drugs can induce immune complex reactions and activate complement cascade, while others can induce direct activation of mast cells and degranulation or activation of complement by non-immune mechanisms. With different types of medications different pathomechanisms are involved. Non-steroid anti-inflammatory drugs are thought to cause reaction due to cyclooxygenase-1 inhibition and overproduction of leukotrienes, blamed for cutaneous and respiratory symptoms. Angiotensin-converting enzyme inhibitors can cause fatal angioedema, which is partially explained with bradykinin excess and impairment of aminopeptidase P and dipeptidyl peptidase IV that are involved in the metabolism of substance P and bradykinin. It remains unknown what additional mechanisms are involved. Radiocontrast media and local anesthetics mostly cause nonallergic hypersensitivity reaction, but in rare cases true allergic reaction can occur. Dextran is known to cause IgG mediated, immune complex anaphylaxis and it is recommended to use human serum albumin as the safest colloid.

KEY WORDS: pseudoallergy, nonallergic hypersensitivity, drug intolerance, drug hypersensitivity, anaphylactoid reaction, allergy-like reactions

INTRODUCTION

Specific intolerance reactions to medications are not based on sensitization of the immune system. For the first time, intolerance to aspirin was described in 1901 by Hirschberg and was termed „idiosyncrasy“. This term is today frequently used for similar reactions to local anesthetics, contrast

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media, natural and artificial food ingredients. Several terms have been used such as idiosyncrasy, intolerance, pseudoallergy and nonallergic hypersensitivity. According to revised terminology from 2003, The European Academy of Allergology and Clinical Immunology has suggested that each condition should be categorized as allergic or nonallergic, and terms that are no longer in use are idiosyncrasy (now hypersensitivity), pseudoallergy (now nonallergic hypersensitivity), and anaphylactoid reaction (now nonallergic anaphylaxis) (1,2).

Pseudoallergy or nonallergic hypersensitivity is a nonimmune hypersensitivity reaction that mimics allergic reaction (3). Two types of pseudoallergy have been traditionally defined: intolerance and idiosyncratic reaction. The pathogenesis of these reactions includes pseudoallergy, idiosyncratic reactions, IgE mediated hypersensitivity, and also elevated IgG antibodies. Pseudoallergy is sometimes called drug intolerance. Clinical symptoms are practically identical to IgE-mediated immediate type symptoms and include angioedema, urticaria, bronchospasm, gastrointestinal signs and anaphylaxis (previously called anaphylactoid reaction). Probably the same effector mechanisms and cells (basophils and mast cells) are involved. However, since there is no evidence for induction of specific immunologic parameters, skin tests and antibody determinations are typically negative (3). The most common nonallergic reactions are to nonsteroidal antiinflammatory drugs (NSAIDs) and hypersensitivity to angiotensin-converting enzyme (ACE) inhibitors. Some reactions to drugs are due to an enzyme defect or deficiency. This is observed in severe hypersensitivity reactions to sulfonamides and aromatic anticonvulsants (4,5). Drug intolerance is a condition encountered in patients that are unable to metabolize a drug due to a defect or lack of the normal enzyme involved in the respective drug pharmacology; this results in an unexpected reaction to a specific drug. An example of intolerance is deficiency of glucose-6-phosphate dehydrogenase and methemoglobinemia as the result of the use of dapsone.

Today, there are new insights in the pathomechanisms of these reactions, and some of them have been more or less clarified.

TYPES OF DRUG REACTIONS

Modern pharmacotechnology has made great effort to increase therapeutic index of drugs by using nanoparticulate vehicle systems. These systems are used to provide slow release or targeted delivery of drugs (6). Nanoparticulate vehicle systems are very useful but also imply a high risk of acute hypersensitive reactions that are not IgE mediated. These reactions are called nonallergic hypersensitivity, are distinguished from type I reaction by Coombs and Gell and have been termed "complement activation-related pseudoallergy" (CARPA) (Table 1). Medications that can cause CARPA are radiocontrast media, some liposomal drugs (Doxil, Ambisome and DaunoXome) and micellar solvents containing amphiphilic lipids (Cremophor EL, the vehicle of Taxol). These agents activate complement system through the classic and the alternative pathways, giving rise to C3a and C5a anaphylatoxins, triggering mast cells and basophils for secretory response. As a result, there is an excessive amount of C3 and C5 anaphylatoxins in the circulation, which can have dramatic cardiovascular sequels (6,7). A new proposal has been given in recent literature to fit CARPA in the classic scheme of hypersensitivity reactions, according to the basic mechanism of mast cell and basophil activation. There are direct and receptor-mediated reactions and therefore there are true IgE-mediated allergy, anaphylatoxin-mediated CARPA and IgE plus anaphylatoxin double triggered reactions (6,7).

Such reactions are primarily caused by 1) certain liposomal formulations of intravenous drugs and imaging agents; 2) infusion liquids containing micelle-forming amphiphilic lipids or synthetic block-copolymer emulsifiers; and 3) iodinated radiocontrast media with limited solubility in water. According to recent literature data, intravenous application of some liposomal drugs, radiographic agents used in diagnostic procedures, micelles or other types of lipid-based nanoparticles can cause acute hypersensitivity reaction in up to 45% of patients. The mechanism of these reactions is activation of the complement system on the surface of lipid particles.

Table 1. Three different groups of medications with capacity of causing complement-activation related nonallergic hypersensitivity reaction (according to Szebeni *et al*.)

Complement-activated nonallergic hypersensitivity reactions
1) Liposomal formulations of intravenous drugs and imaging agents
2) Infusion liquids with micelle-forming amphiphilic lipids or synthetic block-copolymer emulsifiers
3) Iodinated radiocontrast media with limited water solubility

These acute reactions manifest with severe hemodynamic, respiratory and cutaneous changes (8). For example, a drug named paclitaxel (Taxol®) activates complement system in human serum *in vitro*, due to fact that dilution of the injection concentrate in aquagenous solvents resulted in micelle formation and needle like structures with final result of complement activation (9).

Cremophor EL is the main component of micelles and is used as a nonionic emulsifier. These micelles were shown to be 8-22 nm in diameter when analyzed, but *de novo* formation of microdroplets sized 50-300 nm occurred following incubation with human plasma (9). Recent literature data point to the role of lipoproteins in complement activation-related nonallergic hypersensitivity caused by amphiphilic drug carriers (10). Complement activation requires multiple complement and other immune proteins on the activator surface. As mentioned above, Cremophor EL micelles or poloxamer 188 individual molecules when exposed to plasma cause *de novo* formation of abnormally large lipoprotein-like structures. Therefore, this lipoprotein transformation may be the key event in complement activation caused by amphiphilic emulsifiers. Lipoproteins also have a negative

Table 2. Groups of medications, suspected pathomechanism involved, possibility of cross-reactions, safe alternative medication, recommended diagnostic procedure and management, and possible prevention

Group of medication	Suspected pathomechanism	Known cross-reactivity	Safe alternative	Diagnostic work-up	Management and prevention
NSAIDs	True allergic reaction and nonallergic reaction where COX-1 inhibition causes shunting towards leukotriene overproduction, and decrease in the anti-inflammatory prostaglandin PGE2	Possible reaction with all drugs in group	Acetaminophen in single dose <1000 mg	*In vivo* provocation tests: oral, nasal and inhalation test, scratch test, TTL, ITDBG, CAST-ELISA test and combined flowcytometry) basophil activation test with leukotriene determination	Avoidance of nonselective NSAIDs, usage of COX-2 inhibitors, avoidance of artificial and natural salicylates in food
ACE-inhibitors	Nonallergic pathomechanism; role of bradykinin and substance P, and impairment of aminopeptidase P and dipeptidyl peptidase IV	Complete cross-reactivity among all ACEIs, possible reaction with angiotensin II inhibitors	Diuretics, calcium antagonists, beta-blocking agents	None available	Immediate discontinuation of the drug, possible surgical procedure (tracheotomy) in case of severe angioedema
Radiocontrast media	Nonallergic reactions called CARPA reaction due to high osmolarity and water insolubility, activation of complement occurs and C5a causes tryptase activation	Cross-reaction among iodinated contrast media	*In vitro* testing can identify non-cross reacting radiocontrast media	Prick, intradermal skin test, TTL, ITDBG, specific IgE, patch test	Premedication with corticosteroids and antihistamines (efficacy?)
	Allergic reaction caused by - iodinated proteins - specific IgE - T-cell reaction (delayed hypersensitivity reactions)				

Local anesthetics	Majority nonallergic reactions, only 1% true allergy, and mostly presented as type IV reaction	Group cross-reactivity can occur in the same group of anesthetics/ amide or ester type	Based on skin tests and IgE determination, cross reactive agents should be determined	Prick, scratch test, TTL, ITDBG, patch test, *in vivo* exposure test, IgE determination	
Volume expanders	Human serum albumin - non-specific reaction to protein aggregates, in some cases specific immune response to caprylate-modifiate human serum albumin	Not observed	Human albumin is considered to be the safest volume expander	Specific dextran-IgG or IgM	
	Dextran - immune complex mediated anaphylaxis - presence of high IgG (IgM) - dextran reactive antibody and reduction of C1q complement				Hapten inhibition by low molecular dextran- dextran 1 is infused before Dextran 40 or 70

feedback control on complement activation. Lipoproteins play a complex modulatory role in CARPA nonallergic hypersensitivity caused by amphiphilic drug solvents and carriers (10).

It was experimentally shown that intravenous application of liposomes can cause significant pulmonary hypertension in pigs and this represents a model for vasoconstrictive response in the lungs observed as cardiopulmonary distress in humans caused by few liposomal drugs.

The size, composition and administration of liposomes are of great importance, having a striking and different impact on pulmonary vessels and outcome of drug administration varying from minimal impact to lethal outcome (8,11).

It is well known that allergic-like reactions are very common upon vaccination. In the majority of cases, there is absence of immediate hypersensitivity to the vaccine, which can be confirmed by prick-test and intradermal tests with immediate reading (12).

Apart from NSAIDs and ACE inhibitors, some other drug classes have been traditionally classified as elicitors of nonallergic hypersensitivity reactions, such as radiocontrast media, muscle relaxants and local anesthetics. Recently, the immune-mediated pathogenesis has been identified for some of these drugs.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The prevalence of hypersensitivity to NSAIDs manifested as angioedema and urticaria is increasing, ranging from 0.1% to 0.3% (13). The reason why some people react to NSAIDs is not quite explained, and the exact pathogenesis is not clear for all entities, but it is believed that an imbalance in the arachidonic acid cascade, inhibition of prostaglandin synthesis and increase in leukotrienes may play a crucial role (Table 2). Hypersensitivity to NSAIDs manifesting in the airways (rhinosinusitis, polyps, asthma) or skin (urticaria, angioedema) is considered to be the second most common drug reaction (14). There are two types of cyclooxygenase (COX) enzymes, COX-1 and COX-2 (15,16). COX-1 is constitutionally expressed in most tissues such as kidneys and gastrointestinal tract, and is held responsible for the classic pharmacologic side effects of NSAIDs such as renal failure, bleeding and gastric ulcers. COX-2 is present in brain tissue and is induced by proinflammatory factors such as cytokines and

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endotoxin. COX-1 inhibition results in shunting of arachidonic acid metabolism towards the 5-lipooxygenase pathway and results in increased synthesis and release of cysteinyl leukotrienes (13) (Table 2). Selective COX-2 inhibitors are well tolerated by most patients with a history of sensitivity against classic NSAIDs, but cutaneous reactions to highly selective COX-2 inhibitors have also been described (12,13).

However, it is worthy mentioning that NSAIDs by pharmacological mechanism involving the arachidonic acid mechanism can cause exacerbation of or trigger chronic urticaria. About 4% of patients with previous reaction to aspirin may have reaction to COX-2 selective NSAIDs, especially in the group of patients with aspirin sensitive asthma. This group of patients should be advised not to take acetaminophen in a dosage higher than 1000 mg in a single dose due to the fact that acetaminophen is a weak inhibitor of COX-1 enzyme (17).

Facial (periorbital) angioedema is the most common clinical presentation and one third of patients have a mixture of cutaneous (urticaria and/or angioedema) and respiratory symptoms (13). Respiratory symptoms include edema of the upper respiratory tract, rhinorrhea, cough, breathlessness and tearing. The stimulation of leukotrienes such as LTC4, LTD4 and LTE4 causes respiratory symptoms (3).

Three different patient groups are distinguished according to clinical appearance of nonallergic hypersensitivity to NSAIDs (3) (Table 3):

1. Patients with the aspirin or salicylate triad called Fernand-Widal syndrome (Table 4). This syndrome includes intrinsic asthma, nasal polyps, often serum and tissue eosinophilia, and in some cases chronic rhinosinusitis. There are no cutaneous symptoms but life-threatening aggravation of asthmatic and rhinitic symptoms can occur when acetylsalicylic acid or other NSAID is administered (2,18-19). Aspirin nasal challenge is a very safe test with moderate sensitivity and high specificity, and can be used in the diagnosis of aspirin hypersensitivity. The similarities in the reaction between the nose and airways in aspirin-sensitive patients provide compelling evidence for common pathogenic mechanisms for nasal polyps, chronic rhinosinusitis, and bronchial asthma (19). The pathogenic mechanism of Widal syndrome now appears to involve the combined effects of chronic inflammation (causing nonspecific cellular hyperreactivity, particularly of mast cells, basophils and eosinophils), and a pharmacogenetic abnormality of arachidonic acid metabolism in response to NSAIDs. This leads to leukotriene overproduction and a decrease in the anti-inflammatory prostaglandin PGE2 (20). Various aspects of this syndrome such as its clinical features, the cell types and mediators involved, the role of underlying chronic inflammatory processes, the patterns of cross-reactivity between NSAIDs, the major role of LTC4 and of some other mediators such as PGE2 and C5a are described in recent literature.
2. Group of patients with chronic or chronic recurrent urticaria or angioedema that experience aggravation of symptoms if NSAIDs are used. Dyspneic feeling can be present but usually there is no bronchial hyperreactivity or asthma. The reaction is characteristic of acetylsalicylic acid and other NSAIDs (3).
3. Group of otherwise healthy individuals may have anaphylactoid reactions to only one chemically distinct group of NSAIDs such as a pyrazolone derivative, diclofenac, or others (3).

However, cases with bronchial, cutaneous symptoms and severe anaphylactic reaction have been described and patients have reacted to different NSAIDs, including paracetamol (acetaminophen) (21-23). Some kind of genetic predisposition is found in patients with anaphylaxis to pyrazolones, with a significantly higher frequency of HLA-DQ7 as compared to controls (3,24), and in patients with nonallergic anaphylaxis to different classes of NSAID such as pyrazolones, aspirin and others, where an association with HLA-DR11 has been found as compared to subjects tolerant to the respective drugs (3,25).

Also, a distinct entity of NSAID nonallergic hypersensitivity has been observed in atopic patients sensitized to house dust mites. They suffer from allergic rhinitis, severe anaphylactic reactions upon ingestion of mite-contaminated flour, and mostly periorbital angioedema to several NSAIDs (3,26,27).

Some special features of NSAID nonallergic hypersensitivity have been described in a pediat-

Table 3. Nonallergic hypersensitivity to non-steroid antiinflammatory drugs (NSAIDs)

Patient groups according to clinical presentation of nonallergic hypersensitivity to NSAIDs
1) Fernand-Widal syndrome – 'salicylate' triad
2) Worsening of chronic urticaria
3) Nonallergic anaphylaxis to one NSAID

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Table 4. Fernand-Widal syndrome ('salicylate' or 'aspirin' triad)

1) Intrinsic asthma
2) Nasal polyps and chronic rhinosinusitis
3) Tissue and serum eosinophilia

ric group of patients (28). According to these data, the prevalence is low in children aged less than 10 years, but has been estimated to 10% in the group of patients aged 10-20 years. Two theories of aspirin-sensitive asthma are described, i.e. the already mentioned theory of cyclooxygenase pathway and the viral theory explaining the inhibition of cytotoxic lymphocytes by prostaglandin production. Therefore, NSAIDs block PGE2 production and cause the release of cytotoxic lymphocytes. Five different clinical entities have been described: respiratory disease with aspirin sensitivity, aspirin induced urticaria, allergic reaction to aspirin and to NSAIDs, aseptic pneumonitis, and meningitis due to hypersensitivity. The latter are only mentioned as exceptional, as case reports, have never been directly correlated to NSAIDs, and were only described in patients on long-term therapy.

According to the authors, nonallergic hypersensitivity to NSAIDs was found in 13%-50% of pediatric patients with allergic-like reactions and risk factors, personal atopy and age over 8 years. Most children with NSAID nonallergic hypersensitivity tolerate acetaminophen (29).

In cases of aspirin-induced asthma it has been shown that the leukotriene antagonists montelukast and zafirlukast may prevent aspirin-induced bronchospasm (3,30). The authors describe a failure of the leukotriene antagonist zafirlukast to prevent anaphylaxis to ibuprofen in one patient (3,31), and a patient with aspirin triad treated with montelukast developed a life-threatening bronchospasm to diclofenac (3,32). The role of leukotriene modifiers is not established and requires further investigations before they are recommended for this group of patients (18).

The management of these patients includes avoidance of aspirin and all non-selective NSAIDs, use of COX-2 inhibitors, and use of acetaminophen in a dosage less than 1000 mg *per* dose (18).

Thorough history data are obligatory. The only reliable test of the eliciting drug and cross-reactivity is oral provocation test that should be done under close medical supervision (3). Several diagnostic provocation tests can be used, i.e. oral (26,33), inhaled or nasal (19) provocation tests. Besides provocation tests, *in vitro* tests are also available.

The release of sulfidoleukotrienes *in vitro* is detectable by the CAST ELISA test (34). The assay is based on the detection of LTC4, LTD4 and LTE4 by a monoclonal antibody using cellular antigen stimulation test (CAST). The sensitivity of CAST was found to range from 62.5% to 80%, while the specificity was 70%-100% (34,35).

Also, basophil activation test is useful for *in vitro* diagnosis of NSAID hypersensitivity because of its good specificity and positive predictive value in NSAID hypersensitivity (35,36).

Combined test with flowcytometry basophil activation and determination of leukotrienes is useful for *in vitro* diagnosis of hypersensitivity to aspirin and other NSAIDs. NSAIDs induce blood basophil activation *in vitro* in aspirin- and NSAID-hypersensitive patients, and this can be detected by a flowcytometry technique using the CD63 marker, flowcytometry basophil activation test (FAST) assay, in addition to CAST as a leukotriene release test. According to the authors, FAST shows a high percentage of positive reactions, up to 60%-70% when four NSAIDs are tested and even 88% if the test is performed within 1 month of the last clinical drug exposure and reaction. The test has a high specificity, above 90%. The addition of leukotrienes determinations yields additional information in a few isolated cases (35).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

Angiotensin-converting enzyme inhibitors (ACEIs) have been used in the treatment of various cardiovascular diseases. Despite therapeutic benefits of ACEIs, there are several reported side effects, including chronic cough, angioedema and nonallergic anaphylaxis. ACEIs may cause a range of adverse cutaneous reactions (37). These reactions are caused by a combination of factors involved in the synthesis, metabolism and pharmacological activity of bradykinin and des-arginine^{9}-bradykinin (37,38). According to the authors, half of the patients with angioedema have an enzyme defect involved in des-arginine9-bradykinin, which leads to its accumulation (38).

Captopril is most commonly involved. Captopril has a thiol-group and urticarial, exanthematic, bullous and photosensitivity reactions have been described (39,40).

The most common adverse reactions are cough and angioedema typically presented without urticaria. It is estimated that 0.1% to 0.5%, according to some data even up to 0.7% of the patients

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experience angioedema during ACEI therapy (41,42).

Data from emergency wards on angioedema indicate the percentage of ACEI induced cases to range from 25% (43) to 38% (44), with the highest prevalence of angioedema recorded in the group of African-American women.

Angioedema is typically observed within the first weeks of treatment, most patients experience reaction in the first two months, but it may be delayed for months or even years (45). A late onset of angioedema after enalapril is described after 4 months. Late onset of angioedema is often unrecognized. Lip and tongue swelling was the most common airway manifestation. The attacks may occur at irregular, unpredictable intervals under ongoing treatment (46). As in angioedema of other origins, the face and oral mucosa (47-49) are most often affected but isolated visceral angioedema has also been reported (50-52).

The pathogenesis cannot be explained only by the vasodilatory effect (38). Angioedema caused by ACEIs is not immune mediated, and is due to the pharmacological effect of ACE inhibition. Bradykinin is a potent vasodilator and is thought to play a major role in the pathogenesis due to the decreased degradation of bradykinin by ACE-inhibition. During the attack, plasma bradykinin levels are elevated suggesting that this mediator does play a crucial role (53), but also other factors are playing the role since angioedema does not occur regularly after the drug intake and in every patient (46). According to the authors, half of the patients had an enzyme defect involved in the des-arginine9-metabolism (38). Bradykinin may lead to the activation of proinflammatory peptides and local release of histamine, inducing a cough reflex hypersensitivity.

Preliminary studies have shown that patients with a history of developing these side effects have a lower activity of an enzyme called aminopeptidase-P. This enzyme is involved in bradykinin degradation. This defect in enzymatic activity can be partially explained by genetic variation (54,55). Bradykinin and substance P, which are substrates of ACE, cause an increase in vascular permeability and cause tissue edema in animals. Studies indicate that amino-terminal degradation of these peptides by aminopeptidase P and dipeptidyl peptidase IV may be impaired in individuals with ACEI-associated angioedema. Dipeptidyl peptidase IV activity is depressed in individuals with hypertension during acute ACEI-associated angioedema. The degradation half-life of substance P correlates inversely with dipeptidyl peptidase IV antigen during ACE inhibition. Various factors that reduce dipeptidyl peptidase IV activity may predispose individuals to angioedema. Dipeptidyl peptidase IV deficiency predisposes to peritracheal edema when ACE is inhibited through a neurokinin receptor-dependent mechanism (55,56).

Recurrent isolated AE of the tongue is an extremely rare variant of ACEI-induced edema (46,50,51). Risk factors for ACEI-induced angioedema are previous angioedema of any origin and C_1 esterase inhibitor deficiency (57), and use of antibiotics and local anesthetics (58). Surgery and local anesthesia can further aggravate angioedema (58).

The above mentioned drugs do not elicit reaction when used without ACEI. ACEIs may also aggravate anaphylactic and nonallergic anaphylactic reaction (59).

Since the pathogenesis is not quite explained, the diagnosis can only be made based on the clinical finding and medical history; specific diagnostic tests are not available. Oral provocation tests are ethically not acceptable because the severity of the reaction is not predictable, and fatal outcome of laryngeal angioedema has been reported (60).

ACEI-induced angioedema shows class-effect, therefore, there is complete cross-reactivity among all ACEIs (61). Diuretics, calcium antagonists and β-blocking agents are relatively safe alternative for ACEI. Angiotensin II receptor antagonists (AT II blockers) such as losartan potassium are a class of antihypertensives developed in part to eliminate cough and angioedema associated with ACEIs and to act by selective binding to angiotensin II sites. These drugs do not affect local and systemic bradykinin levels. A small percentage of patients with ACEI-related angioedema experience the same problems when switched to angiotensin II blockers. Until the exact cause of both ACEI- and angiotensin II blocker-induced angioedema is determined, angiotensin II blockers should be used with extreme caution in patients with a prior history of angioedema of any origin. Three cases of angiotensin II blocker-induced angioedema have been described (60-62). Losartan was not discontinued after the first episode and resulted in several episodes of angioedema; one severe episode required tracheotomy. The incidence of angiotensin II blocker-induced angioedema questions the theory on the etiology of angioedema and the role of bradykinin in its pathogenesis (62-65).

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When the reaction occurs, drug should be immediately discontinued, even when the first episode is mild. Life-threatening angioedema of the larynx due to continuation of the drug after discrete angioedemas of the face and the tongue that occurred months and years before has been reported. Some patients may experience severe mucosal angioedema and intubation might be necessary in order to prevent fatal outcome. One case report describes a favorable therapeutic effect of C1 inhibitor concentrate administration. Hereditary angioedema is caused by excess of bradykinin formation as a result of C1 inhibitor deficiency, and usually reverses angioedema by C1 inhibitor in less than half an hour. Patients with ACEI-induced angioedema have normal C1 inhibitor values, excess bradykinin is probably important since angiotensin-converting enzyme breaks down bradykinin. The authors conclude that C1 inhibitor was effective in reversing the ACE inhibitor-induced angioedema (66).

RADIOCONTRAST MEDIA

All currently used iodinated contrast media are composed of one (monomers) or two (dimers) triiodinated benzene rings (67,68). Benzene is a toxic water-insoluble liquid. Addition of iodine gives several characteristics: high contrast density, firm binding to benzene molecule and low toxicity. Based on their physical and chemical characteristics, contrast media are classified into ionic high-osmolality and low-osmolality contrast media.

It was considered for years that the pathomechanism of severe immediate reactions cannot be explained by any of the four Coombs and Gell reactions, and reactions were mostly considered as nonallergic anaphylaxis and involving mast cells, basophil histamine and/or vasoactive mediator release mechanisms. Histamine is released *in vivo*, with the peak concentration correlating with the reaction severity (69,70). Complement activation has been shown *in vivo* and *in vitro* in patients that have the reaction and in those with no reaction. Although clinical signs suggest a major role of histamine, it is still a matter of debate (70). *In vivo* histamine release could be an effect of hyperosmolarity, chemical toxicity of the molecule administered, complement activation by anaphylatoxins, or immune mechanism mediated by immunoglobulins. Histamine is released from mast cells and/or basophils (70). Mast cells also participate through tryptase release (69,70). Tryptase has been shown to activate complement system *in vitro*, resulting in C5 activation; therefore complement activation could be the consequence of tryptase release rather than histamine release (70).

The responsible antigen in the presence of iodinated contrast medium could be iodinated serum proteins (71), and in case of drugs with low molecular weight different parts of the molecule responsible for different patterns of IgE binding. Recently, papers showing evidence for positive specific IgE and correlation between histamine release and reaction severity have been published (67,72). According to data, 2.4% to 3.1% of cases had positive IgE-RIA (72).

The low osmolality iodinated contrast media can be subdivided into nonionic monomers (iohexol, iopamidol), ionic dimers (ioxaglate) and nonionic dimers (iodixanol) (67,68).

Contrast media are generally well tolerated; only 0.1%-0.4% of patients receiving high-osmolar ionic and 0.02%-0.04% of those receiving low-osmolar non-ionic contrast media will develop severe hypersensitivity reaction (67). The incidence of mild and moderate reaction is higher in high osmolarity media, but the incidence of severe reactions is equal (68). Nonallergic anaphylactic reactions are more common with high osmolarity media, and cardiovascular decompensation with low osmolarity media.

Reactions are more frequent with ionic than with nonionic material (67,72,73). Reactions after the administration of nonionic contrast media are usually less severe (67).

Risk factors for nonallergic hypersensitivity reactions include asthma (5 times), previous reaction (4-6 times), renal and cardiovascular disease, and beta-blocker intake. Reaction usually occurs within 20 minutes and can be mild (skin rash, itching, nasal discharge, nausea and vomiting), moderate (facial or laryngeal edema, bronchospasm, dyspnea, tachycardia or bradycardia), and severe (arrhythmias, hypotension, laryngeal and pulmonary edema, seizure, syncope and death) (68).

According to literature data, the risk of adverse event is 4%-12% with ionic contrast medium and 1%-3% with nonionic material (73). The risk of severe adverse reaction is 0.16% with ionic contrast medium and 0.03% with nonionic material. Death rate is almost equal for both groups, and is 1-3/100 000 contrast administration (72,73). In pediatric population, 80% of nonallergic hypersensitivity reactions are mild, 5% moderate and 15% severe (74). Nonallergic hypersensitivity to low-osmolality contrast media in children are rare

and according to published data occur in 0.18% of patients receiving contrast media (74).

More than 90% of immediate reactions after the administration of nonionic contrast media are non-IgE mediated reactions, therefore investigations are usually not performed (67,73). Contrast media are typically thought to induce urticaria and angioedema by a nonallergic pathomechanism. As mentioned above, in some patients IgE-antibody-mediated mechanisms have been identified (72,75). Therefore, the ENDA/EAACI group has recently established the value of skin tests in order to look for IgE-mediated reactions (67).

Since nowadays nonionic contrast media are widespread, severe adverse reactions are less frequently seen (73,76).

All iodinated contrast media may elicit immediate type hypersensitivity reaction (within 5-10 minutes of administration) or delayed type that occurs more than 1 hour after the application (76,77). Late adverse reactions to iodinated contrast media have been reported in 2% to 5% of patients exposed to these media.

Late adverse reactions are defined as reactions occurring 1 h to 1 week after contrast medium injection (78). The prevalence of these reactions is still uncertain and their pathophysiology is not fully understood. Late reactions appear to be more frequent when nonionic dimers are used (78).

The so-called “late reactions” can present as maculopapular exanthema, hypersensitivity syndrome with exanthema, eosinophilia and fever, flu-like disease, headaches, gastrointestinal disturbances (nausea, vomiting), musculoskeletal pain, and are mainly not immune mediated (3). They should be neither confused with the clearly defined “late phase” of the IgE-mediated allergy nor with T cell mediated “delayed type” allergy. Delayed type hypersensitivity with maculopapular febrile exanthemas has been reported (79).

Delayed hypersensitivity reactions occur more than 1 h after contrast medium administration. Delayed reactions to iodinated contrast media are most likely caused by immune reactions to drugs. They have been reported in 0.5%-2% of recipients, mainly as mild to moderate skin reactions that can elicit different clinical features such as maculopapular exanthematous and urticarial/angioedematous types. Most of the reactions appear after a latency of 3 h to 2 days and disappear within 1 week. The incidence of more severe reactions is extremely low. Major risk factors for delayed reactions are previous contrast medium reaction, a history of allergy, IL-2 treatment and being of Japanese descent. The pathogenesis of these delayed reactions is still unclear but a significant proportion of these reactions seem to be T-cell mediated (78,80-82). The involvement of T cells is suggested by positive skin test as well as positive proliferative responses to the drugs *in vitro*. A high degree of cross-reactivity was observed with other iodinated contrast media. Moreover, 50% of these patients reported another drug hypersensitivity, suggesting a predisposition to immune reactivity in some patients (81). The management of these reactions is symptomatic and most of these reactions have a self-limited course (78).

There is a possibility of immune cross-reactivity in the group of iodinated contrast media, and due to this fact all contrast media are usually avoided. Evaluation of patients with contrast medium-associated exanthema should always include patch, prick and intradermal skin testing in order to ensure that patients with delayed type are not missed (76,83). Cross-reactivity among iodinated contrast media results from the presence of contrast medium specific T cells that show a broad cross-reactivity pattern (83). *In vitro* testing can identify non-cross reacting contrast media (83). Studies have also demonstrated that patients may receive alternative iodinated contrast medium despite a history of contrast medium-induced exanthema (76,83). An interesting observation of a patient with urticaria that had a non-immediate positive intradermal test has been recently published; it was explained by the fact that immediate reactions are mostly IgE mediated, but also require collaboration of activated T cells, as previously observed in penicillin allergy. T cells participate in immediate reaction and are documented with positive lymphocyte transformation test (67,84).

Skin tests, both prick and intradermal test, have been used and positive tests are rarely reported, mostly in patients with severe reactions (85,86). False-negative results of testing could be due to low molecular weight of iodinated contrast media and a theoretical need for haptenization to become complete allergens (67).

Classic approach to previous iodinated contrast medium reactors is premedication with corticosteroids and antihistamines and use of low osmolality iodinated contrast media (67,68,85,86).

The American College of Radiology recommends administration of prednisolone 50 mg orally (0.5-0.7 mg/kg orally for children) 13 h, 7 h and 1 h before contrast medium administration,

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and diphenhydramine 1 h before in a dosage of 50 mg orally (1.25 mg/kg orally for children) (74). The efficacy of premedication is debated. It is recommended to exclude true allergic reaction (87).

LOCAL ANESTHETICS

Local anesthetics are divided into ester type and amide type. Adverse reactions to local anesthetics are relatively common, but true IgE-mediated hypersensitivity is extremely rare, particularly to the more commonly used amide group. The majority of adverse reactions have a nonallergic pathogenesis (88,89). Allergic reactions are extremely rare (about 1% of adverse reactions) and are mostly presented as type IV allergic reaction, more common with ester-type anesthetics (90-94). There are only few reports on cases of documented true IgE mediated reactions to local anesthetics (90-94). Skin tests offer a reliable method for exploring immediate allergy to confirm or rule out immediate allergy to local anesthetics (90-94). In cases of true allergic reaction to amide type, diagnostic test should be done because cross-reactivity can occur in the same group of anesthetics (93,94).

Although some reports documented immediate IgE reaction to amide type anesthetics, it is little known about cross-reactivity in this group (95,96). Prick testing should be done (97).

Type IV reaction is predominantly observed to ester-type anesthetics, but it can also occur to amide type (93-94); there are only few cases of such reactions to amide derivatives resulting in infiltrated plaques.

Local anesthetics are known to elicit T-cell reactions after epicutaneous application, namely contact dermatitis. In addition, adverse reactions like urticaria and angioedema are rather common after submucosal or subcutaneous injection. The pathogenesis of these side effects, which appear frequently hours after application, is unknown, but is thought not to be IgE-mediated, since immediate skin tests are mostly negative. Delayed appearance of urticaria and angioedema after subcutaneous application of local anesthetics may be related to T cell- mediated sensitization, which might be detected by patch testing or lymphocyte transformation test (98). Nonallergic anaphylaxis during spinal anesthesia was observed with dibucaine (99).

MEDICATIONS USED IN GENERAL ANESTHESIA

Hypersensitivity reactions, whether IgE-mediated (anaphylaxis) or non-IgE-mediated (nonallergic anaphylaxis), occurring during general anesthesia remain a major cause of concern for anesthesiologists, since these reactions remain usually unpredictable and may be potentially life-threatening, even when appropriately treated.

The incidence of anaphylactic reactions in general anesthesia is between 1:5000 and 1:25000 anesthetics. During anaphylactic reaction, mast cells release proteases such as tryptase, histamine and vasoactive mediators. Nonallergic reactions can be caused directly by the release of histamine and other mediators from mast cells and basophils, and they do not depend on the interaction of IgE antibodies with the antigen. The most frequent agents that cause reactions during anesthesia are neuromuscular blocking agents (among them most frequently rocuronium and succinylcholine), some general anesthetics, antibiotics, blood and blood products, opioids and latex. Increased tryptase concentration in serum is a marker for systemic mast cell activation (100). Apart from latex, muscle relaxants are one of the major causes of anaphylaxis during general anesthesia (101). IgE-antibodies directed against quaternary ammonium ions have been identified (102). Based on skin tests and IgE determinations, cross-reactive patterns could be identified and patients were successfully treated with test-negative agents. Few attempts have been made to induce tolerance in sensitized patients (103).

According to published data, the majority (according to authors, 10 of 18 patients) experienced an IgE-mediated anaphylactic reaction to neuromuscular blocking drugs during anesthesia, later verified by detection of specific IgE and elevated levels of mast cell tryptase (104,105). Rocuronium is one of the most frequently involved agents (105-107).

VOLUME EXPANDERS

All colloid volume expanders have the risk of causing nonallergic hypersensitivity reactions and nonallergic anaphylaxis. Currently used colloids are albumin, hydroxyethyl starch (HES), dextran and gelatin.

Albumin is a 69 kDa protein purified from human plasma. HES is synthesized by partial hydrolysis of amylopectin plant starch and hydroxyethylation of glucose molecules. Dextran is composed of glucose polymers. Gelatine is synthesized by hydrolysis of bovine collagen. All artificial colloids are polydispersed molecules in a range of sizes.

Human serum albumin is considered to be a relatively safe volume expander since nonallergic

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anaphylactic reactions have been reported much less than with artificial colloids (108,109). As reported, recent data were analyzed, with albumin as the reference volume expander; the incidence of nonallergic anaphylactic reactions was 4.51 after hydroxyethyl starch administration, 2.32 after dextran, and 12.4 after gelatin (109,110) (Table 5).

Table 5. Incidence of hypersensitivity reactions to different types of volume expanders

Type of volume expander	Incidence of hypersensitivity reactions (human serum albumin as reference colloid) (%)
Human serum albumin	1
Hydroxyethyl starch	4.51
Dextran	2.32
Gelatin	12.4

According to literature data, nonallergic anaphylaxis occurred after infusion of pastered plasma of human serum albumin and reaction resulted from nonspecific reaction to protein aggregates and in some cases from specific immune response to caprylate-modifate human serum albumin (109,111).

The symptoms of dextran-induced nonallergic hypersensitivity reactions range from skin reactions to severe circulatory shock severity grades I-IV. Dextrans are another example where the mechanism of a reaction initially classified as nonallergic anaphylaxis could be clarified. This is called immune complex-mediated anaphylaxis. The presence of high IgG-dextran reactive antibody, reduction of C1q complement factor and histopathologic findings in lungs indicate immune complex anaphylaxis (112).

Clinical dextrans such as Dextran 40 and Dextran 70 are associated with nonallergic anaphylaxis caused by dextran-reactive IgG antibody (113). Dextran-reactive IgG or IgM antibodies were identified (114) and hapten-inhibition by a low molecular dextran resulted in a considerable decrease of severe life-threatening events (112,115). According to the authors, if Dextran 1 is infused immediately before the clinical dextran, it significantly reduced the incidence of severe reaction (113). Very rarely, severe reactions occurred despite hapten inhibition (116). Dextran and gelatins should be avoided in patients with a known history of drug allergy (117).

CONCLUSIONS

Several daily used drugs can elicit drug reactions including non-immune mediated reactions that may often be mistaken for allergic reactions in daily life. The severity of these reactions can range from mild to life-threatening severe reactions such as angioedema and anaphylaxis. These reactions are most commonly caused by NSAIDs, ACE inhibitors, radiocontrast media, local anesthetics, plasma expanders and several agents used in general anesthesia. The pathomechanisms of these reactions have not yet been fully understood for every incriminated agent, but it has been shown that the same mediators found in allergic reactions can be responsible and are involved in non-immune mediated hypersensitivity reactions, e.g., histamine, mast cells, tryptase and complement system.

Detailed history data, *in vivo* and *in vitro* testing should be performed to exclude allergic reaction. Most of these reactions are mild and have a self-limited course, however, some may require surgical intervention or intensive care treatment, like in severe cases of ACEI-induced edema or anaphylaxis.

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