



Allergic drug reactions

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Abstract

Objective: This review addresses the most recent published literature regarding drug allergy, in order to provide physicians with a background for a better understanding of this problem of great relevance for public health.

Sources of data: The sources of data for obtaining the original and review articles published in the last 10 years were MEDLINE, Pubmed and Lilacs. The articles chosen for this review relate drug allergy to immunological mechanisms, epidemiology, clinical and laboratory evaluation, skin lesions, clinical management, and re-exposure to the drug.

Summary of the findings: Allergic reactions represent one third of adverse drug reactions. They are considered rare but with high morbimortality. Gell & Coombs' definition has been useful for classifying some types of drug allergic reactions; however, some still remain without classification because of poor knowledge of the mechanisms involved. The existence of T cell subpopulations with diverse characteristics reveals the complexity of the subject and, at the same time, elucidates several questions raised about it. It was recently postulated a new concept of chemically inert drug presentation to T cells, restricted to the major histocompatibility complex, but in a non-covalent and labile way. In clinical practice, without adequate laboratory tests, it is difficult to correlate clinical symptoms and immunological mechanisms. *In vitro* and *in vivo* skin tests have been employed in cases of suspected drug allergy reaction. However, there are very few commercially available reagents.

Conclusions: Drug allergy constitutes an important problem in adverse drug reactions because of its potential of morbidity and mortality. It is necessary to emphasize the relevance of pharmacovigilance during treatment of patients, as well as the identification of possible immunological mechanisms involved in the events, through laboratory tests and detailed history and clinical evaluation.

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Epidemiology

Adverse drug reactions are any reactions that result from the use of a certain medication (e.g.: allergic reactions). Allergic reactions (ARs) to drugs are adverse events that do not result from known toxicological properties of the drug, but from immune reactions to this drug or to its metabolites.¹ In general, it is believed that ARs account for approximately 3% to 6% of all hospital admissions, occurring in 10 to 15%

of hospitalized patients.² ARs represent one third of adverse reactions³ and have been an important cause of morbidity and mortality, being regarded as a public health problem.³⁻⁵ The major problems related to ARs lie in the fact that they are unpredictable, that there is no animal model for their study, and that the metabolism of a drug varies from individual to individual.^{1,4}

The cost of ARs for health services is often underestimated, since most reactions occur in outpatients.¹ The use of alternative antibiotics in patients who have already had adverse reactions to beta-lactams often results in a higher treatment cost, poor effectiveness, and higher toxicity.¹

Among the drugs that cause allergic reactions we have penicillin. This may be partly explained by previous exposure of individuals to penicillin-containing products, such as foods from treated animals and vaccines containing antimicrobials.⁶

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Viral infections may be a risk factor for the development of AR.⁷⁻¹⁰ In HIV-positive patients, ARs are at least ten times more frequent than in HIV-negative patients.^{8,10} For instance, sulfonamide therapy in HIV-patients is associated with high incidence of adverse reactions (greater than 40%).¹⁰ The incidence of skin reactions due to the oral administration of ampicillin or amoxicillin during an acute episode caused by the Epstein-Barr virus (infectious mononucleosis) is elevated among children and young adults.⁹ Familial susceptibility to AR also has been reported,¹¹ and may be related to different metabolic pathways of the drug, and to the antigenic process.

In children, the drugs most commonly associated with ARs are beta-lactams (82%) and sulfonamides (5%).¹²

Drug-induced anaphylactic reactions are believed to occur in approximately 0.95% of the general population.¹³⁻¹⁵ Although anaphylactic reaction to penicillin is a rare event, this drug is still accountable for around 75% of fatal cases of anaphylaxis in the United States every year.¹⁶

Thong *et al.*,² in a prospective study conducted between 1997 and 1999, in a general hospital of Singapore, assessed approximately 90,910 admissions, of which 366 were due to adverse reactions, and of these 72 were AR (19%). Antimicrobials, especially beta-lactams, specifically penicillins, and antiepileptic drugs accounted for 7% of allergic reactions. Most reactions occurred later through skin disorders, especially as a maculopapular rash, but involvement of other tissues and organs (e.g.: liver and blood cells) was also observed.

Multiple drug allergy is rare and is characterized by an individual's susceptibility to reactions to antibiotics of different chemical groups or to other drugs; however, except for beta-lactams, the mechanisms of other drugs do not seem to include immune mechanisms of histamine release.¹⁷

Classification

Adverse drug reactions can be grouped into three categories: type A, which are predictable and common, and related to the pharmacological activity of the drug; type B, which are unpredictable and uncommon, and depend on patient characteristics; and type C, which are related to the statistical increase in the incidence of a disease in patients exposed to a medication as compared with its basal frequency in unexposed individuals.^{16,18,19} Approximately 80% of adverse drug reactions are of type A, whereas type B reactions correspond to approximately 6 to 10%. Albeit more rare, type B reactions account for most spontaneous notifications received by drug surveillance systems in the USA, given their peculiar and unpredictable character.^{16,18,19} Type B reactions include symptoms of intolerance to drugs, idiosyncratic reactions and allergic reactions. They are often identified after the medication has been commercialized during the drug surveillance process.^{1,16} "Allergic reaction to drugs" is used when the reaction includes specific circulating antibodies and/or specifically sensitized lymphocytes.^{19,20} Pseudoallergic reactions occur when manifestations similar to those of an allergic reaction are

observed, and when there is no immunological specificity.^{3,19,20}

ARs are grouped according to the classification of Gell & Coombs.^{16,20} Type I or immediate reactions are mediated by specific IgE antibodies associated with mast cells and basophils, and their clinical manifestations may include anaphylaxis²¹ or urticaria/angioedema.²²⁻²⁴ In type II or cytotoxic reactions, medications and/or their metabolites may nonspecifically adhere to the surface of erythrocytes, platelets, neutrophils, allowing for antibody binding with consequent cell lysis via complement system (C) activation mechanisms or via antibody-mediated cytotoxicity.²⁰ Type III hypersensitivity, also known as "serum sickness" occurs due to the deposition of immune complexes in blood vessels, basement membranes of the skin or glomerulus, activation of the C system, increase in vascular permeability and neutrophil recruitment. Tissue damage is caused by the release of lytic enzymes by neutrophils and C activation.^{20,25} Type IV or late hypersensitivity is caused by the interaction of antigen with inflammatory and/or cytotoxic lymphocytes in the absence of antibodies.^{20,26-28}

Although this pathophysiological classification is useful for some allergic reactions, it does not usually allow us to infer, based on clinical symptoms, which immune mechanism is involved, as occurs in rashes, toxic epidermal necrolysis and in Stevens-Johnson syndrome.²⁶⁻²⁸

Pichler & Yawalkar²⁶ suggested a subdivision of allergic reactions into "real" allergic reactions (penicillin, sulfonamide), autoimmune reactions (D-penicillin, procainamide), pseudoallergic reactions (acetylsalicylic acid) and pharmacological interference by drugs with immune cell functions, such as production of cytokines, signal transduction (cyclosporin A, thalidomide).

Immune mechanism

For a molecule to be regarded as immunogenic it should have a molecular weight (MW) greater than 1,000 Da, as occurs with heterologous serum proteins (e.g.: equine serum against snake venom), enzymes (e.g.: chymopapain) and hormones (insulin). Most medications have a low MW (e.g.: penicillin); thus, they react as haptens, binding to a carrier protein (often autologous, such as albumin) for induction of a specific immune response. Some of these drugs have to be metabolized before they bind to the carrier molecules.^{4,6,20}

Sensitivity to a certain drug occurs much easier with intermittent and repetitive administrations (e.g.: penicillin or insulin) than with continuous administration. Sensitive patients can react to minimum doses, especially if given parenterally (regarded as the most immunogenic route). However, topical administration (cream, ointment, eyedrops) may result in sensitization and consequent allergic reaction.⁶

Despite a wide variety of antimicrobial agents, beta-lactams, especially penicillin and cephalosporin, are the most frequently prescribed drugs, and the ones that most commonly cause allergies.^{6,29,30}

All penicillins have a beta-lactam ring and a thiazolidine ring (Figure 1) and the distinction between them is made based on the nature of the side chain.^{29,30} The beta-lactam ring is unstable, and when it opens it quickly forms amide bonds with amino groups of lysine residues from surrounding proteins. Approximately 95% of penicillin metabolites conjugated to proteins contain a penicilloic group which, due to its amount, is called "major determinant". Other conjugates include penicillinate, penicilloic acid, penicillanyl and are known as "minor determinants."^{16,30} Minor determinants, due to their variety, make laboratory investigation more complex.²⁸

Cross-reactivity is a crucial problem with drug hypersensitivity. It is characterized by an immune response to a medication in an individual who was previously sensitive to another similar drug. Reactivity to side chains, as well as to the main structures has already been demonstrated in type I hypersensitivity;³⁰ however, for the activation of T cells to take place in late hypersensitivity reactions, the central structure of the drug seems to be essential, and the presence of side chains is not enough.³⁰⁻³²

Although immediate allergic reactions to penicillin are more frequent, other types may also occur.^{6,16,20,28} In case of penicillin-induced hemolytic anemia, IgG is the predominant antibody isotope, and cell lysis results mainly from the interaction of immunoglobulin with macrophage receptors at extravascular sites.³³ The massive administration of penicillin with daily doses greater than 10 million units for over one week seems necessary to induce hemolysis.^{29,33} The reaction may last for weeks while there is a sufficient number of penicillin-coated erythrocytes and specific antibodies in the circulation.^{29,33}

Sulfonamide metabolites, such as sulfamethoxazole hydroxylamine, may be toxic to the immune system, but are also considered to be immunomodulatory.⁷ In micromolar concentrations, the metabolite can lead CD8+ T cells to apoptosis (programmed cell death), whereas CD4+ T cells remain viable and produce a different immune response to the drug. Chronic immune hyperactivation in response to pathogens may increase the levels of interferon-gamma (IFN- γ). This cytokine, in turn, will induce keratinocytes to express molecules of the major histocompatibility complex (MHC) class II.⁸ The presentation of drugs by MHC II molecules on the surface of keratinocytes may lead CD4+ T cells to apoptosis.⁴

As previously mentioned, the hypothesis for presentation of the drug to the T cell, known as hapten and prohaptent, are respectively based on the fact that drugs or their metabolites, if chemically reactive, may bind to carrier molecules or to the cell surface and interact with cells of the immune system and/or with antibodies.²⁰

The participation of T cells in allergic reactions to chemically inert drug structures has been shown in the last few years.^{10,31} A new model of interaction between drug, MHC molecule and T cells, known as pharmacological interaction with immune receptors (p-i concept), has been proposed.³¹ According to this hypothesis, the structure of the drug would bind to the peptide-MHC complex on one side

and to the T cell receptor on the other side. Thus, the structure of the drug would determine the binding, which albeit labile, would be enough to induce the activation of T cells. This type of mechanism is observed with sulfamethoxazole, lidocaine, mepivacaine, celecoxib, carbamazepine,³¹ and clinical manifestations may include maculopapular rash, contact dermatitis, acute generalized exanthematous pustulosis and toxic epidermal necrolysis.³¹

Under physiological conditions, one can suppose that low-affinity T cell receptors prevent any damage that could occasionally result from the presentation of the drug to the cells.^{26-28,31-34} A signal, known as "danger signal" is necessary for the activation of the immune system, as for instance, damage to kidney cells caused by the toxic effect of a drug metabolite, excessive stimulation of immune response during infections by viruses such as HIV and Epstein-Barr, periods of clinical activity of autoimmune diseases, such as Sjögren's syndrome or systemic lupus erythematosus.²⁸

T cell receptors contain two chains (alpha and beta) bound together by disulfide bonds, whose function is to recognize peptides linked to MHC molecules class I or II.³⁵ Another type of T cell receptor, containing chains gamma and delta, represents 5 to 15% of T cells in human peripheral blood, being predominantly found in the epidermis, intestinal epithelium, female reproductive system and lungs.³⁵ Little is known about how they recognize the antigens.³⁵ Pichler & Yawalkar²⁶ found out that nearly all human T cells have alpha and beta receptors, and that most clones are MHC-restricted; only 5 to 10% are able to recognize the drug in an MHC unrestricted way.

The histological section of the skin of patients with drug-induced maculopapular exanthema revealed lymphocyte infiltrate containing CD3+ T cells (40 to 70%), with predominance of CD4+ and CD8+ T cells at the dermoepidermal (perivascular) junction, a variable number of eosinophils and some neutrophils.²⁷

CD4+ and CD8+ T cells detected in skin lesions were found to have cytotoxic properties.^{26-28,34} Both cell populations contain cytolytic proteins (perforins and granzyme B), which can form pores in target cells and eventually destroy them.^{26-28,34} Another apoptosis-inducing mechanism concerns the binding of Fas molecules to their ligand on the surface of cells.³⁵ The Fas molecule belongs to the same family of TNF receptors, found in the membrane of several cells, and if bound to its ligand, either in soluble form or expressed in the membrane of activated cytotoxic T lymphocytes, causes apoptosis of the cell that originated it. The fact that cells that express Fas molecules on their surface may bind to their ligand in the soluble form explains the large number of lysed cells, even in the absence of cell infiltrate, in diseases such as toxic epidermal necrolysis.³⁴

Hepatic involvement and bullous lesions often are associated with the activity of CD8+ T cells.³⁴ Cytotoxicity mediated by CD4+ T cells may contribute to the hydropic degeneration of the basal cell layer, as in maculopapular exanthemas; however, no bullae are formed. Bullous lesions occur when a drug combined with a peptide-MHC class I

complex in keratinocytes is presented to specific CD8+ T cells.^{28,34}

Contrary to most T helper cell responses, where Th1 or Th2 cytokines predominate, heterogeneous cytokine response patterns are observed in skin reactions to drugs.²⁸ In this case, we may find, IFN-gamma secreting CD8+ T lymphocytes and IL-5 secreting CD4+ T lymphocytes.²⁸ The presence of IL-5, a cytokine whose role is to regulate the maturation, differentiation and activation of eosinophils, may explain eosinophilia in most of these patients.

Since different subpopulations of drug-specific T cells can be found in inflammatory skin lesions, Pichler *et al.*²⁸ proposed a subclassification of Gell and Coombs type IV reactions. According to them, type IVa would predominantly be determined by a Th1 pattern, similarly to what occurs in the response to tuberculin. Type IVb would comprise the Th2 pattern, with high levels of IL-5, which is responsible for eosinophilia. Type IVc would include cytotoxic CD4+ T cells that contain cytolytic factors found in maculopapular exanthema, and CD8+ T cells, which contain cytolytic factors and, when activated, express FasL, as occurs in bullous exanthema. And finally, type IVd, which would include IL-8 producing T cells, chemotactic factor for neutrophils. In the latter case, there would be accumulation of neutrophils in the lesions and keratinocytes would present IL-8 production, without increasing the expression of MHC molecules class II.

Clinical picture and diagnosis

The clinical manifestations of ARs vary and depend on the immune mechanism and on the organ that is affected. Specific IgE-dependent reactions often develop quickly and may be so intense that they can jeopardize the patient's life, as occurs in anaphylactic shock. ARs can be divided into generalized [a] which depend on the participation of mast cells, including anaphylaxis, urticaria and angioedema, serum sickness (partially); b) fever; c) autoimmune reactions and d) vasculitis], or restricted to an organ [a] skin: allergic eczematous contact dermatitis, photodermatitis, maculopapular rashes, fixed eruptions, bullous exanthema or toxic epidermal necrolysis and cutaneous vasculitis; b) blood: eosinophilia, anemia, granulocytopenia and thrombocytopenia; c) lung: airway obstruction, eosinophilic reactions or infiltrates, fibrosis; d) liver: cholestasis, hepatocellular damage; e) kidney: interstitial nephritis and f) heart]

The time of manifestation of ARs varies according to the immune mechanism involved. They can be classified into: a) immediate – they occur within the first thirty minutes to two hours after drug administration, b) accelerated – between two and 48 hours (urticaria, bronchospasm, fever, nephropathy), c) delayed reactions – 48 after drug intake (skin rashes, fever, serum sickness, hemolytic anemia, thrombocytopenia, nephropathy).

Genetic factors, patient's age, history of previous reactions or even cross-reactions, power and immunogenicity of the drug are risk factors for the development of ARs. The diagnosis of AR should include careful history of the type of

drug given, dose, route of administration, time when lesions developed, and knowledge about other factors that may interfere with its metabolism and also the type of therapy used in its management. Moreover, laboratory investigation is of utmost importance.³⁷

Among severe reactions, anaphylactic shock is of extreme relevance as it may result in death. Other severe reactions include toxic epidermal necrolysis (around 30%), Stevens-Johnson syndrome (5%), hypersensitivity syndrome (10%) and manifestations in other organs, including liver, kidney, lung and blood cells.³

Acute tubulointerstitial nephritis was described after the use of several penicillins, such as methicillin, penicillin G, ampicillin, amoxicillin, nafcillin, oxacillin, dicloxacillin, and piperacillin. However, methicillin seems to be the prototype of this type of reaction.²⁹ In our setting, cases of patients with nephritis caused by intravenous administration of oxacillin have been described.²⁵

One of the major problems related to ARs concerns the identification of the immune mechanisms implicated. Many patients with positive history are not necessarily allergic to the drug used.³⁰ On top of that, different drugs often are given concomitantly,¹⁷ and the commercial availability of specific *in vivo* and *in vitro* tests is limited. Provocation tests, which are widely used, are complex and usually not sensitive enough,³ or do not have a predictive value for clinical use.³⁸

In patients with previous clinical history of anaphylactic reaction, management is complex, since the absence of diagnosis and the subsequent occurrence of anaphylaxis may be fatal; on the other hand, misdiagnosis may impose unnecessary restrictions.³⁹ There are also those patients who somatize their symptoms, which reinforces that physicians should make a distinction between "allergy" from "nonallergy."³⁹

As previously mentioned, the pathophysiological mechanism involved in adverse drug reactions is often unknown. However, all reactions resulting from the intake of a drug or food are regarded as an allergy.

Reactions to nonsteroidal anti-inflammatory drugs (NSAID) have been increasingly frequent and exemplify the comment made above. These reactions usually are characterized by acute angioedema and/or acute urticaria, either localized or generalized, or by bronchospasm. NSAIDs control the synthesis of prostaglandins (PG) by inhibiting the action of cyclooxygenase (COX), which is essential for the conversion of arachidonic acid to PG. Once this pathway is blocked, the lipoxygenase pathway is used, with consequent increase in the synthesis of leukotrienes (powerful inflammatory mediators). Leukotrienes act upon blood vessels and promote important vasodilatation with transudation and extravasation of intravascular fluid; intense and sustained contraction of the smooth bronchial muscles and overproduction of mucus by seromucous glands.⁴⁰

COX enzymes seem to play a central role in the sensitivity to acetylsalicylic acid (ASA). There are two isoforms: COX-1 and COX-2, which are encoded by different genes. COX-1 is

the constitutive form, which is widely distributed all over the body and is involved in homeostasis. COX-2 is induced during inflammation and increases the synthesis of inflammatory prostanoids. ASA, indomethacin and piroxicam, even in low doses, inhibit both enzymes, especially COX-1.⁴¹ Other salicylates that are well tolerated by patients with ASA-induced asthma have virtually no action on COX-1 and have half the power of ASA to inhibit COX-2. Nimesulide and meloxicam are selective COX-2 inhibitors and are well tolerated by these patients. New and highly selective COX-2 NSAIDs have been under investigation.⁴¹

Reactions to NSAIDs are called anaphylactoid reactions because they do not result from the immune mechanism involved. These patients usually have family history of reactions to NSAIDs, dose-dependent clinical symptoms, and symptoms within the first two hours after drug administration. The same patient may have intolerance to other drugs of the same group, and this has been incorrectly defined as cross-reactivity: ASA, diclofenac, dipyron, and more rarely, acetaminophen.⁴¹

For the assessment of patients with type I allergic reactions, skin tests with immediate reading and the measurement of serum levels of specific IgE by RAST (radioallergosorbent test) are the most commonly used tests. Skin tests (prick tests) can be easily performed, are safe and allow quick results. However, they are only useful in the evaluation of sensitivity to penicillin, barbiturates and muscle relaxants. The lack of information on the factors that determine the allergic reaction and the commercial unavailability of reliable allergen extracts explain its restricted use. In case of previous history of severe reaction, the test must be performed in a hospital in a room where resuscitation equipment is at hand. In patients suspected of having allergic reaction to penicillin, the penicilloic conjugate bound to poly-L-lysine (PPL) allows assessing sensitivity to major determinants, and the recently prepared penicillin mixed with "minor determinants" (penicilloate, benzylpenicilloate, benzylpenicilloate) are recommended,^{17,37,38} however, they are not commercially available in our setting.

Regarding skin tests for major and minor determinants of penicillin, negative predictive values of 97 and 99% are respectively estimated, which means that if the test yields a negative result, the patient can tolerate the drug without being exposed to immediate allergic reaction.³⁷

Patch tests used to investigate the participation of T cells in skin disorders should be performed especially in patients with suspected diagnosis of contact dermatitis. It is a time-consuming procedure in which two readings are made at a 48-hour interval. In addition to the restriction of the drugs used, the skin must be intact for the test. The difficult interpretation of results is due to the fact that different populations of T cells might be involved.²⁸

Another test that is only used in research is the assessment of T cell proliferation in a culture medium at nontoxic concentrations of the suspected drug.^{42,43} The complexity and the time necessary for the test impose restrictions on its use.⁴² Nyfeler & Pichler⁴² assessed 923 patients with suspected drug allergy, and found positive

results for the lymphocyte transformation test in 78/100 patients. The diagnostic sensitivity and specificity of the test was estimated at 78 and 85%, respectively. Some authors claim that negative results on this test do not rule out drug allergy and that positive results do not necessarily mean that the patient will be sensitive to a new exposure to the drug.²⁸ Despite these remarks, it is a promising test for the laboratory diagnosis of drug allergies.^{9,42,43}

Another test used in research concerns the assessment of serum IL-5 levels secreted by peripheral blood mononuclear cells in the presence of the analyzed drug.⁴⁴ This test has a diagnostic sensitivity of 92%, which is higher than that of the lymphocyte transformation test (78%) or of the patch tests (55%). This test is not performed as a routine practice.

In case of drug-induced hemolytic anemia, the direct antiglobulin test (DAT) can be used to check for the presence of sensitized red blood cells, that is, coated with antibodies. As there exists a risk of losing the bound antibodies during cell washing, which could decrease the positivity of the test, it is suggested that the analysis of antibodies in the patient's serum be made using the indirect antiglobulin test (IAT).^{29,33}

If drug-induced nephritis is suspected, parameters such as eosinophilia, proteinuria, hematuria and leukocyturia may be useful in the laboratory diagnosis.²⁵

Table 1 summarizes some of the laboratory tests used to determine the immune mechanisms of ARs, according to the classification proposed by Gell and Coombs.

As previously mentioned, it is important to determine whether immune mechanisms are implicated so that the appropriate therapy can be implemented. Also, the differential diagnosis between allergic reaction and pseudoallergic reaction should be established based on information collected from the anamnesis (previous personal or family history), general physical examination (lesions, vital signs) and laboratory findings (specific and/or complementary).^{37,38}

Reexposure to the drug

Solensky *et al.*⁴⁵ evaluated 46 patients with previous history of allergy to penicillin and negative skin test results at the beginning of the study. The patients were submitted to three courses of oral treatment with penicillin V potassium (250 mg, three times a day for 10 days in each course), and no sensitivity was observed to any of the regimens. This led the authors to conclude that single assessment using the skin test has a negative predictive value for the subsequent administration of the drug, allowing for the reduction of unnecessary use of alternative antibiotics.

Macy & Burchette⁴⁶ discovered that only 9.3% of patients with previous history of adverse reactions to penicillin had a positive skin test result, and of these, 33% showed reaction to oral penicillin. According to the authors, a positive skin test for penicillin is useful in predicting adverse reactions to penicillins, while a negative test result means that the drug may be safely used.

Table 1 - Laboratory tests used to determine the immune mechanisms of ARs according to the classification proposed by Gell and Coombs

Reaction type	Immune mechanisms	Laboratory tests
I (immediate)	IgE - basophils and/or mast cells	Skin and intradermic tests, RAST, basophil histamine release
II (cytotoxic)	IgG and/or IgM - antigens in the cells membrane	Coombs' test (IAT, DAT)
III (immune complexes)	IgM an/or IgG complexes - soluble antigens	Complement (C3, C4), immunohistochemical test (IIF, DIF)
IV (late)	T Cells	Epidermal (patch) and intradermic test, <i>in vitro</i> lymphocyte transformation, cytokines measures

RAST = radioallergosorbent assay (serum specific IgE); IAT/DAT = indirect antiglobulin test/direct antiglobulin test; IIF/DIF = indirect immunofluorescence/direct immunofluorescence test.

Another study⁴⁷ assessed the incidence of sensitization to penicillin after the skin test in individuals with or without previous history of allergy to penicillin. A sensitization of 2.5% was observed, which was defined as the conversion of a negative result to a positive test result within a four-week period, without any drug administration. With regard to individuals who had a positive skin test right at the beginning of the study, some of the associated factors included having asthma, being female, and having atopic disease. Macy *et al.*⁴⁸ assessed 568 patients exposed to oral penicillin, with a negative skin test. Of these patients, only 11.4% had some adverse reaction to penicillin in a four-year evaluation period, and none of the reactions was severe. No difference was noted as to the frequency of adverse reactions in patients with reactive and nonreactive skin test results.

Clinical management

Treatment of AR consists of immediate discontinuation of the medication and implementation of usual therapy to treat clinical manifestations. In patients with severe reactions, the distinction between the implicated mechanisms is often unnecessary. Anaphylactic or anaphylactoid reactions (regardless of the presence of specific IgE antibodies) require a similar emergency treatment.

The emergency treatment of these severe reactions should be initiated with the subcutaneous administration of a millesimal solution, which has proven effective in most cases.⁴⁹ In a recent study, Simons *et al.*⁵⁰ have confirmed the results previously obtained with children showing that the intramuscular administration of epinephrine into the lateral face of the thigh warrants higher serum concentrations and a more prompt therapeutic response than the subcutaneous administration into the deltoid muscle. Furthermore, its use has been better tolerated.⁴⁸ An antihistamine (given intramuscularly) and a corticosteroid (given intravenously) should be added to this treatment.¹³

Pretreatment with corticosteroids or with H1 antihistamines is still controversial.¹⁴ These substances have been indicated for patients at high risk of having adverse reactions to iodine contrast media.⁵¹

The clinical management of patients with AR is complicated because the pathophysiology and predisposing factors for these reactions are unknown.¹⁶ Whereas for type A reactions, the change in the dose prior to its readministration may be sufficient, the clinical management of AR relies on the elucidation of etiologic mechanisms.¹⁶ When diagnostic tests are inconclusive, an alternative medication should be used.¹⁶

Patients with reactions to NSAIDs, especially those with asthma and/or rhinitis, benefit from the discontinuation of drug treatment, restriction on foods that are rich in natural salicylates (tomato, strawberry) and from the continuous use of cysteine leukotriene receptor antagonists.⁴¹ In special cases in which the continuous use of NSAIDs is necessary and there is no substitute, "desensitization" is recommended. In this case, the patient is exposed to increasing doses of NSAIDs, at regular intervals of 20 minutes, until symptoms appear or the desired therapeutic dose is achieved, which should be then maintained uninterruptedly. Continuous administration leads to the elimination of mediators and allows the patient to stay asymptomatic in spite of receiving NSAID. This state of tolerance is lost when the regular use of NSAID is interrupted.⁵²

Desensitization when there is an IgE-dependent mechanism is a relatively safe procedure, and should always be performed at a hospital. It is indicated in cases in which alternative treatments are not possible.⁵³

Patients with previous history of severe allergic reactions, even those which are not mediated by IgE, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis, hemolytic anemia, and nephritis, should have the use of the implicated medications interrupted and should not be submitted to skin tests.³⁰

When adverse reaction to local anesthetics, often used in dental treatments, is suspected, it is necessary to distinguish these reactions from vagal reactions, overdosing, injudicious use of intravenous injection, or associated vasoconstrictor effect (e.g.: epinephrine). Local anesthetics related to adverse reactions belong to two chemical groups: benzoic acid esters and amides, without any reaction between them. In situations in which the suspected drug is not known, the skin test should be performed for either of the anesthetics, so that the drug can be released for use.⁵¹

Conclusions

Allergic reactions are an important part of adverse events that result from the exposure to drugs and their potential of morbidity and mortality. The necessity of systematized notification of ARs to the department of drug surveillance by the professionals involved in the treatment of the patients is of paramount importance. The cost of ARs for health services is often underestimated, since most reactions occur in outpatients. The fact that the implicated immune mechanisms are not totally clear hinders the prevention of new events, not allowing patients regarded as "allergic" to benefit from efficient and safe drugs, which explains the use of more expensive alternatives. The skin test to assess immediate hypersensitivity is useful for IgE-mediated allergic drug reactions. There is growing evidence that T cells can interact with a drug when it is not chemically active or bound to a carrier molecule. The new model proposed for T cell presentation is based on the hypothesis that a drug interacts with peptides associated with molecules of the human major histocompatibility complex by binding to them. Although the binding is labile and noncovalent, it is enough to activate T cells. The type of clinical manifestation will depend on the effector actions of different T cell subpopulations found in lesions.

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