WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 4, Issue 2, Feb., 2023

A MODERN VIEW ON THE PROBLEMS OF DIAGNOSING DRUG ALLERGIES

Razikova I. S.,
Baibekova V. F.,
Shorustamova S. S.,
Solieva H. N.,
Kuziev G. E.,
Kayumova S. Sh.
Tashkent Medical Academy Republican Scientific and Specialized Allergological Center Uzbekistan, Tashkent

Abstract

In recent years, the safety of pharmacotherapy has acquired particular relevance for practitioners [1]. As the number of drugs used to treat various diseases increases, the risk of drug allergies in patients also increases. Drug allergy develops no more often than other manifestations of adverse drug reactions, but its main danger lies in insufficient predictability [2]. The prevalence of LA, according to various studies, ranges from 1 to 30% [3]. The constant growth of drug allergy is facilitated by the widespread self-medication, the simultaneous use of several drugs without taking into account their interaction in the body, the ignorance of doctors about cross-reactions of drugs, the increase in the consumption of biologically active additives and food products with preservatives and dyes, and the increase in the use of drugs as preservatives (acetylsalicylic acid for preserving vegetables, penicillin for preserving meat during transportation), the use of antibiotics in animal feed [4].

According to the World Allergy Organization (WAO, 2012), adverse drug reactions occur in 10% of the world's inhabitants and 20% of hospitalized patients. Approximately 10% of adverse drug reactions are unpredictable drug hypersensitivity reactions, which can be severe and even life threatening. Such reactions are associated with high mortality (up to 20% of deaths due to anaphylaxis are provoked by medications [5]. As a result of LA to penicillins, about 300 people die every year, and the frequency of allergic reactions ranges from 1 to 10%, mortality is 0.002% of cases [6] .

Drug allergy is characterized by the occurrence of hypersensitive reactions to drugs that have an immune mechanism of development. In such reactions, antibodies and/or activated T cells are directed against drugs or their metabolites [7]. Theoretically, allergic reactions can be caused by all drugs, but the most common causes are antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs

(NSAIDs), anesthetics. The risk of developing drug allergy, its clinical features depend on the individual properties of the immune system, the dose of drugs, the duration of treatment, the route of administration, the sex of the patient, as well as on the unique HLA signs that are being described more and more often.

Non-immune (pseudo-allergic) forms of hypersensitivity reactions to drugs is possible , often having identical clinical manifestations [8]. Non-immune variants of adverse reactions to drugs can have a different genesis, for example: non-specific degranulation of mast cells or basophils with the release of histamine (radiocontrast agents, vancomycin), changes in the metabolism of arachidonic acid (non-steroidal anti-inflammatory drugs - NSAIDs), pharmacological effects of substances that cause bronchospasm (beta-blockers) [9].

The immune reaction develops after a period of sensitization either by the active substance or by an "inert" substance (fillers, stabilizers) used in drug preparation technology. Sensitization can occur with any route of administration of the drug: oral, parenteral or topical. The rate of development of sensitization depends on the route of administration of the drug. Local application and inhalation application most often and quickly causes sensitization, but less often leads to the development of life-threatening conditions. Intravenous administration sensitizes somewhat less than intramuscular and subcutaneous. For example, parenteral administration of β-lactam antibiotics is more likely to cause anaphylaxis than oral agents [10].

Clinical manifestations of drug allergy are diverse and may affect all organs and systems. According to the mechanism of development, they proceed according to four types of allergic reactions: I - IgE - mediated (anaphylactic), II - cytotoxic, III - immunocomplex, IV - cell-mediated (P. Gell , R. Coombs , 1975).

Immediate allergic drug hypersensitivity reactions are based on overproduction IgE antibodies by antigen-specific B-lymphocytes. Binding of specific IgE antibodies to high-affinity receptors on the surface of mast cells and basophils, their interaction with the drug antigen leads to the release of preformed mediators (histamine, tryptase), tumor necrosis factor and newly formed mediators (leukotrienes , prostaglandins, kinins , cytokines) [11] . These mediators can be used as diagnostic biomarkers for drug hypersensitivity. Clinically, these reactions manifest themselves in the form of urticaria, angioedema , rhinitis, conjunctivitis, bronchospasm , gastrointestinal disorders or anaphylaxis, anaphylactic shock [12]. Their development can be observed with the use of foreign sera, beta- lactam antibiotics, sulfonamides, analgesics , NSAIDs [13]. Second type medicinal allergic reactions - cytotoxic . It is based on the interaction of predominantly IgG or IgM with an antigen fixed on cell membranes, followed by the development of complement-mediated damage to these cells [14].

Clinically, it is manifested mainly by immunopathological reactions from blood cells, for example, immune hemolytic anemia [15]. The occurrence of some clinical forms of drug allergy may be due to immunocomplex reactions (type III according to Gell and Coombs). They are based on the formation of immune complexes, their deposition in the vascular bed on the membranes of the endothelium of small-caliber vessels, followed by the occurrence of tissue damage and microcirculation disorders [16]. Immunocomplex reactions proceed with the involvement of complement in the pathological process, the resulting anaphylotoxins C3a and C5a cause the release of histamine, proteolytic enzymes, and vasoactive amines from mast cells and basophils. This mechanism is leading in the development of serum sickness, vasculitis, systemic lupus erythematosus, glomerulonephritis , the Arthus phenomenon , and some exanthems of medicinal origin [17]. The most common cause of the immune complex variant of drug allergy is the use of antibiotics, sera, vaccines, sulfonamides, anesthetics, NSAIDs, modern immunobiological preparations (drugs based on monoclonal antibodies) [18]. However, special attention has been focused in recent years on delayed allergic reactions to drugs that are mediated by T-lymphocytes. The most common target for drug-responsive T-lymphocytes is the skin, but other organs may be involved. First, the drug antigen is processed by dendritic cells, then the antigen is transported to the regional lymph nodes, where it is presented to T cells. Subsequently, antigen-specific T- lymocytes migrate to the target organ, after exposure to the antigen, they are activated and secrete pro-inflammatory cytokines that cause the development of inflammation and tissue damage [19]. Clinically delayed drug hypersensitivity reactions most often manifest as symptoms of skin lesions: the occurrence of an pruritic maculopapular rash, fixed drug rashes, vasculitis , toxic epidermal necrolysis , Stevens -Johnson syndrome , generalized bullous fixed drug rashes, acute generalized eczematous pustulosis , and symmetrical drug-associated intertriginous and flexor exanthemas [20]. Internal organs can also be involved in the pathological process (in isolation or in combination with skin symptoms, resulting in hepatitis, kidney damage, hypersensitivity pneumonitis , cytopenias [21].

Often, allergic reactions to medications can occur with the participation of several mechanisms simultaneously. It should be noted that the same drug can trigger various immunological mechanisms, which is most likely due to the individual characteristics of the patient himself and his immunological reactivity. The presence of a period of sensitization necessary for the formation of antibodies or sensitized cells in the human body determines the fact that drug allergy manifestations never develop at the first dose of the drug. In addition, it allows safe administration of the drug for 4–5 days if

it is known that the patient has not previously taken this drug or cross-reacting substances [22].

The issue of specific diagnosis of drug allergy remains relevant and not fully understood at present. To date, there is not a single scientifically based method that would reliably detect sensitization to a drug and their metabolites. The main role in the diagnosis of drug allergy is given to a thorough and detailed collection of allergological and pharmacological anamnesis. A carefully collected clinical history is of fundamental importance in the diagnosis of drug allergy [23]. The list of questions can be considered classic: it is important to establish the sequence of occurrence of symptoms, their duration and the relationship with the use of drugs, to which hypersensitivity reactions are presumably developed; evaluate the time interval between drug intake (last dose) and the onset of a reaction, the effect of discontinuation of treatment on the dynamics of symptoms, as well as the results of past use of other drugs of the same class [24]. Information about the presence of allergic reactions and diseases in the patient's relatives, including reactions to drugs, is essential. Allergological and pharmacological history data give grounds to suspect the development of a drug allergy or, with a high degree of probability, to reject its presence in patients. It should be taken into account that from 1 to 10% of people with drug allergies have multiple drug intolerance syndrome (intolerance to three or more drugs that are neither structurally nor pharmacologically related) [25]. The practitioner and the patient may well be satisfied with the results of targeted elimination tests (cancellation of the drug even in doubtful cases of LA) [26]. As you know, the vast majority of drugs are defective allergens - haptens . Each drug undergoes multiple transformations in the body, is metabolized , and only some metabolite, when combined with blood proteins, is the final allergen. The above explains the difficulties in identifying drug allergies (tests are carried out with the parent drug, and unknown metabolites of drugs can cause an allergic reaction). The safest diagnostic methods are laboratory methods. As for laboratory research methods for drug allergies, most modern literary sources emphasize that their choice is determined by the characteristics of clinical manifestations, the severity of systemic and organ-specific symptoms, and the proposed immune mechanism of drug hypersensitivity reactions. In this regard, the list of methods includes hemogram, direct hemagglutination reaction, complement fixation reaction, precipitation reaction, basophilic test, platelet agglutination test, lymphocyte blast transformation reaction, leukocyte migration inhibition reaction, allergenic cell stimulation test based on the release of sulfidoleukotrienes , flow cytofluorometry test , fluorescent method of allergic alteration of leukocytes, determination of antinuclear and

anticytoplasmic antibodies, specific immunological tests, etc. [27]. A thorough clinical study of patients with drug hypersensitivity makes it possible to assess the nature, severity and danger of symptoms and to conduct an adequate laboratory examination [28].

In methods vivo (skin tests, provocative tests), as a rule, are available from economic positions, are clinically informative. However, these tests can be performed no earlier than 4–6 weeks after stopping the drug hypersensitivity reaction, and require compliance with special conditions. This reduces their significance, as it does not allow them to be used in emergency diagnostics and therapy (post-factum diagnostics). In cases where it is not possible to exclude the diagnosis of drug allergy on the basis of anamnestic and clinical data, specific allergological diagnosis should be carried out in specialized centers. It allows you to establish a diagnosis and recommend alternative pharmacotherapy. Allergological diagnostics (skin testing, provocative tests) can be carried out only after the collection of allergic and pharmacological anamnesis data. The question of using an allergological examination to confirm the allergic nature of drug hypersensitivity reactions most often arises in relation to antibiotics, NSAIDs, and anesthetics. Skin tests. Skin testing is a readily available method for diagnosing drug hypersensitivity [29]. However, we did not find information on the presence of standard diagnostic allergens based on drugs in the literature. Prick tests and intradermal tests are especially important in order to identify IgE -dependent mechanisms of drug allergy [30]. Prick tests are recommended for the initial screening study [31]. Intradermal tests can be performed with negative results of prick tests, they are quite informative in cases of development of immediate hypersensitivity reactions to beta- lactam antibiotics, heparin, in some cases - with delayed reactions. Patch tests (skin patch tests) and/or intradermal tests are performed to detect evidence of the possible development of T-cell-mediated delayed-type drug hypersensitivity reactions [32]. In some cases, negative results of skin testing are due to the fact that it is not the drug itself that has immunogenic properties, but its metabolites. In these situations, drug challenge tests may be used to confirm the diagnosis. Medication provocative tests. They are the "gold standard" for identifying the drug that caused the development of hypersensitivity reactions [33]. Provocative testing with a drug thought to be the cause of the side effect may confirm or exclude the diagnosis of a drug hypersensitivity reaction. Such tests are carried out no earlier than one month after the initial drug allergic reaction, only by specially trained personnel in specialized centers who are experienced in the early detection of hypersensitivity reactions and are ready to provide adequate medical care in case of life-threatening conditions [34]. A contraindication for a provocative test is

the presence of a life-threatening drug hypersensitivity reaction (anaphylactic shock, other systemic allergic reactions, severe skin reactions such as Stevens -Johnson syndrome, toxic epidermal necrolysis , vasculitis). The methods of administration of the suspect drug during the provocation test are in principle the same as for the initial administration. At the same time, preference is given to the oral route of its administration, which is associated with a lower risk of hypersensitive drug reactions when the drug is administered per os [35].

This approach in a significant proportion of cases helps to ensure the correct diagnosis. In the acute phase of the resulting hypersensitivity reaction, it facilitates the decision to continue or stop the ongoing treatment, which could provoke the formation of a drug hypersensitivity reaction.

Patients who have had a drug allergy are contraindicated for life using the medication that caused it. Persons who have suffered severe allergic reactions, drug treatment must be prescribed strictly for health reasons. Before prescribing a drug, it is required to carefully study the chemical composition and properties of the drug, the presence of cross-reactions with other medicines and food products. Particular attention should be paid to data on the presence of so-called hidden allergens in complex preparations containing different chemical groups, but having the same name. Only a careful collection of allergic, pharmacological and nutritional history can prevent the occurrence of drug allergies.

Literature

1. Kolodiychuk E. V., Grudina E. V., Malashenkova T. E. Drug allergy // Medical Bulletin of the North Caucasus. - 2007. - T. 6. - No. 2. - S. 70-75.
2. Drug Allergy S.B. Shabykeeva , A.T. Altymysheva , S.I. Kalyuzhny, N.A. Toktogulova , T.M. Sooronbaev .
3. Allergology. Clinical guidelines / Ed. R. M. Khaitova , N.I. Ilyina. - M.: GEOTAR-Media. -2009. - S. 256.
4. Pukhlik B.M. Drug allergy and side effects of drugs in allergology / B.M. Pukhlik , A.P. Viktorov, S.V. Zaitsev. Lvov, 2008, p. 108.
5. WAO Allergy White Paper 2011–2012: Abstract / ed. acad. R.I. Sepiashvili , T.A. Slavic. M.: Medicine - Health, 2011. 12 p.
6. Shabykeeva S. B. et al. Drug allergy // Bulletin of the Kyrgyz-Russian Slavic University. - 2014. - T. 14. - No. 12. - S. 126-129.
7. Demoly P., Adkinson NF, Brockow K., Castells M., Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler W., Sanchez-Borges M., Shiohara T., Thong

BY International Consensus on drug allergy. Allergy 2014; 69(4): 420–437, http://dx.doi.org/10.1111/all.12350 .

8. Dao R.-L., Su S.-C., Chung W.-H. Recent advances of pharmacogenomics in severe cutaneous adverse reactions: immune and nonimmune mechanisms. Asia Pac Allergy 2015; 5(2): 59–67, http://dx.doi.org/10.5415/apallergy.2015.5.2.59 .
9. Ayuso P., Blanca-López N., Doña I., Torres MJ, Guéant -Rodríguez RM, Canto G., Sanak M., Mayorga C., Guéant JL, Blanca M., Cornejo-García JA Advanced phenotyping in hypersensitivity drug reactions to NSAIDs. Clinic Exp Allergy 2013; 43(10): 1097–1109, http://dx.doi.org/10.1111/cea.12140.
10. Kolodiychuk E. V., Grudina E. V., Malashenkova T. E. Drug allergy // Medical Bulletin of the North Caucasus. - 2007. - T. 6. - No. 2. - S. 70-75.
11. Park BK, Naisbitt DJ, Demoly P. Drug hypersensitivity. In: Allergy. New York: Elsevier BV; 2012; p. 321–330, http://dx.doi.org/10.1016/b978-0-7234-3658-4.00020-2.
12. Limsuwan T., Demoly P. Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). Med Clin North Am 2010; 94(4): 691–710, http://dx.doi.org/10.1016/j.mcna.2010.03.007 .
13. Macy E. Practical management of patients with a history of immediate hypersensitivity to common non-beta-lactam drugs. Curr Allergy Asthma Rep 2016; 16(1):4, http://dx.doi. org/10.1007/s11882-015-0584-3.
14. Leach MW, Rottman JB, Hock MB, Finco D., Rojko JL, Beyer JC Immunogenicity/hypersensitivity of biologics. Toxicol Pathol 2014; 42(1): 293–300, http://dx.doi. org/10.1177/0192623313510987.
15. Garratty G. Immune hemolytic anemia caused by drugs. Expert Opin Drug Saf 2012; 11(4): 635–642, http://dx.doi.org/10. 1517/14740338.2012.678832.
16. Rojko JL, Evans MG, Price SA, Han B., Waine G., DeWitte M., Haynes J., Freimark B., Martin P., Raymond JT, Evering W., Rebelatto MC, Schenck E., Horvath C. Formation, clearance, deposition, pathogenicity, and identification of biopharmaceutical-related immune complexes: review and case studies. Toxicol Pathol 2014; 42(4): 725–764, http://dx.doi.org/1 0.1177/0192623314526475.
17. Clark BM, Kotti GH, Shah AD, Conger NG Severe serum sickness reaction to oral and intramuscular penicillin. Pharmacotherapy 2006; 26(5): 705–708, http://dx.doi. org /10.1592/phco.26.5.705.
18. Koransky R., Ferastraoaru D., Jerschow E. Single nonsteroidal anti-inflammatory drug induced serum sickness-like reaction to naproxen in a patient able to tolerate both aspirin and ibuprofen. J Allergy Clin Immunol Practice 2016; 4(1): 160–161, http://dx.doi.org/10.1016/j.jaip.2015.07.019 .

19. Koransky R., Ferastraoaru D., Jerschow E. Single nonsteroidal anti-inflammatory drug induced serum sickness-like reaction to naproxen in a patient able to tolerate both aspirin and ibuprofen. J Allergy Clin Immunol Practice 2016; 4(1): 160–161, http://dx.doi.org/10.1016/j.jaip.2015.07.019 .
20. Bircher AJ, Scherer K. Delayed cutaneous manifestations of drug hypersensitivity. Med Clin North Am 2010; 94(4): 711–725, http://dx.doi.org/10.1016/j.mcna.2010.04.001 .
21. Ghane Shahrbaf F., Assadi F. Drug-induced renal disorders. J Renal Inj Prev 2015; 4(3): 57–60, http://dx.doi. org/10.12861/jrip.2015.12.
22. Stepanova E.V. Modern aspects of diagnosis and treatment of drug allergies / E.V. Stepanova // Attending physician. 2009. No. 4. P. 17–24.
23. Brockow K., Przybilla B., Aberer W., Bircher AJ, Brehler R., Dickel H., Fuchs T., Jakob T., Lange L., Pfützner W., Mockenhaupt M., Ott H., Pfaar O. , Ring J., Sachs B., Sitter H., Trautmann A., Treudler R., Wedi B., Worm M., Wurpts G., Zuberbier T., Merk HF Guideline for the diagnosis of drug hypersensitivity reactions. Allergo J Int 2015; 24(3): 94–105, http://dx.doi.org/10.1007/s40629-015-0052-6 .
24. Demoly P., Adkinson NF, Brockow K., Castells M., Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler W., Sanchez-Borges M., Shiohara T., Thong BY International Consensus on drug allergy. Allergy 2014; 69(4): 420–437, http://dx.doi.org/10.1111/all.12350 .
25. Omer HM, Hodson J., Thomas SK, Coleman JJ Multiple drug intolerance syndrome: a large-scale retrospective study. drug Saf 2014; 37(12): 1037–1045, http://dx.doi. org /10.1007/s40264-014-0236-x.
26. Pobedennaya G.P. The value of the resources of modern laboratory diagnostics in the practice of a clinician-allergist / G.P. Pobednaya , F.T. Solyanik , P.K. Boychenko et al. // Clinical Allergology and Immunology. 2010. No. 2. P. 70–75.
27. Brockow K., Przybilla B., Aberer W., Bircher AJ, Brehler R., Dickel H., Fuchs T., Jakob T., Lange L., Pfützner W., Mockenhaupt M., Ott H., Pfaar O. , Ring J., Sachs B., Sitter H., Trautmann A., Treudler R., Wedi B., Worm M., Wurpts G., Zuberbier T., Merk HF Guideline for the diagnosis of drug hypersensitivity reactions. Allergo J Int 2015; 24(3): 94–105, http://dx.doi.org/10.1007/s40629-015-0052-6 .
28. Bircher AJ Symptoms and danger signs in acute drug hypersensitivity. Toxicology 2005; 209(2): 201–207, http://dx.doi. org /10.1016/j.tox.2004.12.036.
29. Rive CM, Bourke J., Phillips EJ Testing for drug hypersensitivity syndromes. Clinic Biochem Rev 2013; 34(1): 15–38.
30. Bircher AJ Symptoms and danger signs in acute drug hypersensitivity. Toxicology 2005; 209(2): 201–207, http://dx.doi. org /10.1016/j.tox.2004.12.036.

31. Kränke B., Aberer W. Skin testing for IgE -mediated drug allergy. Immunol Allergy Clin North Am 2009; 29(3): 503–516, http://dx.doi.org/10.1016/j.iac.2009.04.003 .
32. Brockow K., Garvey LH, Aberer W., AtanaskovicMarkovic M., Barbaud A., Bilo MB, Bircher A., Blanca M., Bonadonna B., Campi P., Castro E., Cernadas JR, Chiriac AM, Demoly P ., Grosber M., Gooi J., Lombardo C., Mertes PM, Mosbech H., Nasser S., Pagani M., Ring J., Romano A., Scherer K., Schnyder B., Testi S., Torres M., Trautmann A., Terreehorst I.; ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs — an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013; 68(6): 702–712, http://dx.doi.org/10.1111/all.12142 .
33. Rerkpattanapipat T., Chiriac AM, Demoly P. Drug provocation tests in hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol 2011; 11(4): 299–304, http://dx.doi. org/10.1097/ACI.0b013e328348a4e9.
34. Bousquet PJ, Gaeta F., Bousquet-Rouanet L., Lefrant JY, Demoly P., Romano A. Provocation tests in diagnosing drug hypersensitivity. Curr Pharm Des 2008; 14(27): 2792–2802, http://dx.doi.org/10.2174/138161208786369731 .
35. Aberer W., Bircher A., Romano A., Blanca M., Campi P., Fernandez J., Brockow K., Pichler WJ, Demoly P.; European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003; 58(9): 854–863, http://dx.doi.org/10.1034/j.1398-9995.2003.00279.x.