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ALLERGIC REACTIONS AND MEDICINAL PRODUCTS: CONTEMPORARY PRESENTATIONS

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ABSTRACT

More than 7% of the population suffers from drug allergies. Cases of severe life-threatening allergic reactions have been reported. The review presents modern views on the mechanisms of development of drug immune hypersensitivity, describes the main clinical forms and existing methods for diagnosing drug allergies. Specific diagnosis of drug allergy is carried out using in vivo tests (prick tests, intradermal testing, patch tests, provocative tests) and in vitro (determination of specific IgE to drugs, basophil activation tests, leukocyte blast transformation reactions, quantitative determination of cytokines and other proteins , such as granzyme and tryptase in peripheral blood).

Keywords: drug allergy; allergy to medications; diagnosis of drug allergy; drug hypersensitivity reactions.

However, not all of these methods are available in real clinical practice; the list of commercial kits for diagnosing drug allergies is limited. That is why, when managing patients, it is important to rely on the data of anamnesis and general clinical examination, to take into account the available information about the association of drug allergy and infection with herpes group viruses, especially in the child population, about the presence of a hereditary predisposition to the formation of some forms of drug allergy.

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. This problem is very relevant for practical health care, since more than 7% of the population suffers from drug allergies. In addition, severe life-threatening allergic reactions may develop, requiring hospitalization and long-term treatment. Immunological reactions to drugs (drug hypersensitivity reactions) are considered in category B of adverse drug reactions, the mechanism of which is associated with an abnormal response to drugs. This distinguishes them from type A reactions, which can occur in any patient and, as a rule, are associated with the main mechanism of action of drugs and their dosage.

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.

Both immune and non-immune (pseudo-allergic) forms of hypersensitivity reactions may develop to drugs, often having identical clinical manifestations. 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).

Drug hypersensitivity reactions, depending on the time of their manifestation from the start of treatment, are divided into immediate and delayed (delayed). Immediate drug hypersensitivity reactions occur predominantly within the first hour (first six hours) after drug administration and are induced mainly by an IgE-mediated mechanism. Their typical symptoms are urticaria, angioedema, rhinoconjunctivitis, bronchospasm, nausea, vomiting, diarrhea, abdominal pain, anaphylaxis. Delayed-type hypersensitivity reactions can occur at any time after 1 hour after drug administration, but usually occur later than 6–72 hours from the start of drug administration and are associated mainly with T-cell mechanisms of the allergic reaction. Their clinical manifestations are very diverse and may include maculopapular exanthema, exfoliative dermatitis, erythroderma, DRESS-syndrome (drug-related eosinophilia with systemic symptoms), toxic epidermal necrolysis, and other bullous reactions. System-wide effects can be represented by the development of hepatitis, nephritis, cytopenia, etc.

Pathogenetic mechanisms of drug allergy development

Drug hypersensitivity reactions have existed for as long as the drugs themselves have existed. Nevertheless, many mechanisms of their formation have not yet been disclosed, and there are no approved diagnostic procedures for a large number of types of drug hypersensitivity reactions. Medicines are capable of causing the development of all types of immunopathological reactions described by P.G.N. Gell and R.R.A. Coombs, but IgE-mediated and T-lymphocyte-mediated reactions are the most frequent of them.

Immediate allergic drug hypersensitivity reactions are based on overproduction of 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). 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, and anaphylactic shock. Their development can be observed with the use of foreign sera, beta-lactam antibiotics, sulfonamides, analgesics, NSAIDs.

The second type of drug allergic reactions is 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. Clinically, it is manifested mainly by immunopathological reactions on the part of blood cells, for example, immune hemolytic anemia.

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. 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 exanthemas of medicinal origin. 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).

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. Clinically delayed drug hypersensitivity reactions most often manifest as skin symptoms: pruritic maculopapular rash, fixed drug rashes, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, generalized bullous fixed drug rashes, acute generalized eczematous pustulosis, and symmetric, associated with intertriginous medications and exanthemas located on the flexor surfaces of the extremities. 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.

It was also noted that several types of immunological reactions may be involved in the development of allergic reactions to pharmacological drugs in the same patient. Thus, the involvement of both IgE-mediated and cell-mediated reactions has been proven in the development of insulin allergy.

Many drugs and/or their metabolites are haptens but bind to proteins to form a complete antigen. Such newly formed antigens can cause the development of both IgE-mediated and T-cell-mediated drug hypersensitivity reactions.

Of great interest are modern studies indicating an undoubted relationship between the risk of developing both immediate and delayed allergic drug reactions with genetic factors. This is evidenced, in particular, by the identified relationship between Stevens-Johnson syndrome, toxic epidermal necrolysis induced by carbamazepine, and the HLA-B * 1502 antigen, as well as the association of IL-4 and IL-10 gene polymorphisms with immediate drug hypersensitivity reactions. to beta-lactam antibiotics.

In recent years, it has been established that viral infections, including all herpesviruses, can provoke a drug hypersensitivity reaction, the appearance of skin rashes, if the drug (most often antibiotics) is used during the infectious process. Clinical manifestations can be quite serious as DRESS syndrome (drug-induced eosinophilia with systemic symptoms) and other systemic manifestations.

Hypersensitivity drug reactions are more likely to occur in patients, including children, with allergic diseases. This may be due to a change in the metabolic functions of the body for the biotransformation of medicinal compounds and, in particular, with a change in the activity of their acetylation, the formation of antigenic determinants when interacting with body proteins.

Clinical manifestations of drug hypersensitivity

As mentioned above, the clinical manifestations of drug hypersensitivity can be immediate and delayed relative to the time of drug administration. In addition, systemic (anaphylaxis, drug fever, serum sickness) and organ-specific variants of drug allergic reactions are distinguished. In modern literature, it is emphasized that the main target organ for drug hypersensitivity is the skin, however, other organs can also be involved in the pathological process: the hematopoietic system (eosinophilia, cytopenia, hemolytic anemia), the respiratory system (rhinitis, bronchospasm, laryngeal edema, eosinophilic pulmonary infiltrate), urinary system (glomerulonephritis, nephrotic syndrome, interstitial nephritis), hepatobiliary system (hepatocellular lesions, cholestasis).

Skin lesions in drug allergies. Skin symptoms are the most common in drug allergy, which is due to the high immune activity of the skin. The rashes are polymorphic in nature. They are accompanied by itching, which is most pronounced in measles-like and scarlet-like rashes.

Maculopapular rash. Papular and/or measles-like rash accounts for 75–90% of drug-induced skin rashes.

The onset of the rash is usually observed 1 week after the start of treatment. In the absence of other manifestations, these rashes are usually not dangerous. The predominant cell type in this case is cytotoxic CD4+ T cells. However, lesions may progress to more serious manifestations, including toxic epidermal necrolysis, which is mediated predominantly by CD8+ cytotoxic T cells. Basically, these skin changes disappear a few days after stopping the drug, which is often accompanied by extensive exfoliation of the epidermis, which can leave areas of depigmentation. The main difficulty in the clinical diagnosis of such pathological conditions is the differential diagnosis with infectious exanthems. Some clinical variants of drug hypersensitivity are realized with a certain combination of infectious agents and drugs. An example is the risk of exanthema when using antibacterial drugs of the aminopenicillin group in patients with an infection caused by the Epstein–Barr virus.

Hives. Currently, it is also considered as a fairly typical variant of drug rashes, but it is still less common in drug allergies than maculopapular rash. It is itchy blisters of various sizes and localizations, disappearing without a trace within 24 (48) hours, sometimes associated with Quincke's edema. Blisters usually appear quite quickly - from several minutes to several hours after taking the drug, they can be a component of anaphylactic reactions, including fatal ones. In some patients, drug urticaria is based on IgE-mediated allergic reactions. However, in most cases of drug hypersensitivity, pseudo-allergic variants of urticaria are observed, which can be caused by NSAIDs, angiotensin-converting enzyme inhibitors, and other drugs. In persons suffering from chronic urticaria, in 30% of cases there is an allergy to NSAIDs.

Angioedema of medicinal origin. It is clinically characterized by rapid development in the area of the lips, eyelids, sometimes auricles, on the back surface of the hands and feet, in the genital area.

Fixed dermatitis. This is an interesting type of drug rash, consisting of one or more elements (erythematous, bullous, plaques) of various shapes and sizes, with clear boundaries. It has been established that they are repeated in the same place every time a certain drug is administered. Discontinuation of the drug is usually accompanied by a reduction in symptoms, but often with residual hyperpigmentation, which makes it easy to identify the affected area. When the antigen is re-introduced, the symptoms recur within about 2 hours, the number of elements

often increases. This clinical variant is usually associated with CD8+ T cells. If the area of skin involvement is small, then the course is usually favorable, however, with a widespread process, the prognosis may be more serious, with systemic symptoms such as fever, arthralgia, which requires differential diagnosis with Stevens-Johnson syndrome.

Acute generalized exanthematous pustulosis (AGEP). One of the most serious forms of drug allergy described in recent years. This pathological condition usually includes an acute fever (above 38°C) and skin rashes in the form of small pustules against the background of erythema, usually appearing within a few hours after the use of causative drugs. Mucous membranes may be involved in the process in 25% of cases, but the course may be quite favorable. Characterized by neutrophilia, moderate eosinophilia. In some cases, swelling of the face and hands is observed, but lesions of the internal organs are generally uncharacteristic. Drugs most commonly associated with AGEP syndrome include beta-lactams, NSAIDs, quinolones, macrolides, calcium channel blockers, and antimalarials such as chloroquine. No convincing genetic markers associated with AGEP have been found.

Drug induced hypersensitivity syndrome (DiHS or DHS), DRESS syndrome (drug rash with eosinophilia and systemic symptoms). These syndromes are drug reactions accompanied by eosinophilia and potentially life-threatening systemic symptoms. They were first described relatively recently, with the use of anticonvulsants. Clinical features include acute onset, rash, fever, and at least one of the syndromes (lymphadenitis, hepatitis, nephritis, pneumonia, carditis, thyroiditis) in association with hematological abnormalities (eosinophilia, atypical lymphocytes, thrombocytopenia, leukopenia). The rash, however, may not always be present and its characteristics may vary greatly from patient to patient. Mortality can reach 10%, most often from liver failure. Typically, the onset of symptoms is delayed by 2–6 weeks from the start of the causative drug, which is an important diagnostic criterion. Symptoms may continue for weeks or months after medication is stopped. The most common drugs associated with DRESS/DiHS are carbamazepine and other aromatic anticonvulsants, sulfonamides, allopurinol, and a number of anti-HIV drugs. According to the mechanism of development, it belongs to type IVb reactions. An important role in the development of this syndrome is assigned to the reactivation of the herpesvirus type 6, as well as other herpesvirus infections (Epstein–Barr virus, cytomegalovirus, herpesvirus type 7).

REFERENCES

1. Офицеров, В.И. Подклассы иммуноглобулина G: возможности использования в диагностической практике / В.И. Офицеров. - Кольцово, 2004. – 35 с.
2. Паттерсон, Р. Аллергические болезни. Диагностика и лечение / Р. Паттерсон, Л.К. Грэммер, П.А. Гринбергер. – М.: ГЭОТАР Медицина, 2000. – 733 с.
3. Порядин, Т.В. Аллергия и иммунопатология / Т.В. Порядин, – М., 1999. – С. 152-166.
4. Пухлик, Б.М. Лекарственная аллергия / Б.М. Пухлик. – Киев, 1989. – 94 с.
5. Скепьян, Н.А. Аллергические болезни / Н.А. Скепьян. – Минск, 2000. – 286 с.
6. Хаитов, Р.М Медицинские стандарты (протоколы) диагностики и лечения больных с аллергическими заболеваниями и нарушениями иммунной системы / Р.М. Хаитов. – Москва, 2001. – 118 с.
7. Хаитов, Р.М. Клиническая аллергология / Р.М. Хаитов. – М., 2002. – 423 с.

8. Sharipova G. I. The effect of dental treatment-profilactics on the condition of oral cavity organs in children with traumatic stomatitis // Тиббиётда янги кун. Бухара. – 2022. – № 5 (43). – С. 103-106. (14.00.00; № 22)
9. Шарипова Г. И. Эрта ёшдаги болалар травматик стоматитлар билан оғриганда оғиз бўшлиғи микрофлорасининг иммуно-микробиологик жиҳатлари // Биология ва тиббиёт муаммолари. Самарқанд. – 2022. – № 2 (136). – С. 296-298. (14.00.00; № 19)
10. Sharipova G. I. Light and laser radiation in medicine // European journal of modern medicine and practice. Belgium. – 2022. – Т. 2. – №. 1. – С. 36-41. (Impact factor: 5.71)
11. Sharipova G. I. The use of flavonoid based medications in the treatment of inflammatory diseases in oral mucus //Asian journal of Pharmaceutical and biological research. India. – 2022. – Т. 11. – №. 1. – С. 2231-2218. (Impact factor: 4.465)
12. Sharipova G. I.Changes in the content of trace elements in the saliva of patients in the treatment of patients with traumatic stomatitis with flavonoid-based drugs // Journal of research in health science. Iran. – 2022. – Т. 6. – № 1-2. – С. 23-26. (Scopus)
13. Sharipova G. I. Paediatric Lazer Dentistry //International Journal of Culture and Modernity. Spain. – 2022. – Т. 12. – С. 33-37.
14. Sharipova G. I. The effectiveness of the use of magnetic-infrared-laser therapy in traumatic injuries of oral tissues in preschool children //Journal of Academic Leadership. India. – 2022. – Т. 21. – №. 1.
15. Sharipova G. I. Discussion of results of personal studies in the use of mil therapy in the treatment of trauma to the oral mucosa //European journal of molecular medicine. Germany. – 2022. – Т. 2. – №. 2. – С. 17-21.
16. Sharipova G. I. Peculiarities of the morphological structure of the oral mucosa in young children // International journal of conference series on education and social sciences. (Online) May. Turkey. – 2022. – С. 36-37.
17. Sharipova G. I. Dynamics of cytological changes in the state of periodontal tissue under the influence of dental treatment prophylactic complex in young children with traumatic stomatitis // Multidiscipline Proceedings of digital fashion conference April. Korea. – 2022. – С. 103-105.
18. Шарипова Г.И. Травматик стоматит билан оғриган болаларда стоматологик касалликларни комплекс стоматологик даволаш ва уларнинг олдини олишни баҳолаш // Ўзбекистонда миллий тадқиқотлар: даврий анжуманлар: 18-қисм. Тошкент. –2021. – С. 14-15.