DRUG ALLERGIC REACTIONS: CURRENT VIEWS (REVIEW)

BAKHROMOVA BARNO ZOKIROVNA
Samarkand State Medical University
Department of pharmacognosy and pharmaceutical technologies
barnobaxromova93@gmail.com
ALIBAYEVA YULDUZ RAHMANOVNA
Termiz Abu Ali Ibn Sina Technical College of Public Health is a teacher of pharmacology
MUMINBOYEV DIYORBEK JASURBEK OGLU
Student of group 304 of the Faculty of Pharmacy of Samarkand State Medical

Annotation

More than 7% of population suffer from drug allergy. Cases of heavy life-threatening allergic reactions are well known. In this review current considerations of mechanisms of drug immune hypersensitivity development are presented, the main clinical forms and methods of diagnosing drug allergy are described. Drug allergy is diagnosed with specific in vivo tests (skin prick test, intradermal test, patch test, provocation tests) and in vitro tests (determination of specific IgE to medications, test for basophil activation, reactions of leucocyte blast transformation, quantitative determination of cytokines and other proteins, e.g. granzyme and tryptase in peripheral blood). However, not all of these methods are available in real clinical practice, the list of commercial kits for diagnosis of drug allergy is limited. Therefore, it is especially important in patient management to rely on history-taking and general clinical examination data, to consider the available information on association of drug allergy and infections caused by viruses of herpes-group, especially in children population, on hereditary predisposition to some kinds of drug allergy.

Key words: drug allergy; diagnosing drug allergy; drug hypersensitivity reactions.

Abstract

Drug allergy is characterized by hypersensitivity reactions to pharmacological agents, having an immune mechanism of development. In these reactions antibody and/or activated T cells are directed against medications or their metabolites. This problem is rather urgent for practical healthcare, as over 7% of people suffer from drug allergy. Moreover, heavy life-threatening allergic reactions may develop demanding hospitalization and long-term treatment. Immunologic reactions to drugs (reactions of drug hypersensitivity) are considered among unfavorable reactions to drugs, category B, whose mechanism is associated with abnormal response to medications. This distinguishes them from type A reactions, which may be in any patient, and, as a rule,

are connected with the main mechanism of drug effect and its dosage. Theoretically allergic reactions may be induced by all medicines, however the most common cause of them are antibiotics, unticonvulsant preparations, nonsteroidal anti-inflammatory drugs (NSAID), anesthetics. The risk of drug allergy, its clinical characteristics depend on individual properties of the immune system, drug dose, treatment duration, the route of administration, patient's sex, and also on the unique HLA-signs, which are described in increasing frequency. Immune and nonimmune (pseudoallergic) forms of hypersensitivity reactions can develop to the medicinal preparations, often having identical clinical manifestations. Nonimmune variants of side-effects to the drugs may have various genesis, for example, nonspecific degranulation of mast cells or basophils with histamine release (radiocontrast agents, vancomycin), change of the arachidonic acid metabolism (NSAID), pharmacological action of the substances, causing bronchospasm (beta-blockers). Drug hypersensitivity reactions are divided into immediate and delayed depending on the time of their manifestation after starting the treatment. Immediate drug hypersensitivity reactions develop mainly within an hour (the first six hours) after medication intake and are predominantly induced by IgE-mediated mechanism. Their typical symptoms are urticaria, angioneurotic edema, rhinoconjuctivitis, bronchospasm, nausea, vomiting, diarrhea, pain in the abdomen, anaphylaxia. Delayed allergic reactions may be realized at any time an hour after the drug introduction, but usually occur 6–72 h after the medication intake and are connected mainly with a T cell mechanism of allergic reaction. Their clinical manifestations are diverse and may include maculopapular exanthema, exfoliative dermatitis, erythrodermia, DRESS-syndrome (drug related eosinophilia with systemic symptoms), toxic epidermal necrolysis, and other bulleos reactions. General systemic effects may comprise development of hepatitis, nephritis, cytopenia, etc.

Pathogenetic mechanism of drug allergy development

Drug hypersensitivity reactions have been exisiting as long as medications themselves. Nevertheless, many mechanisms of their formation are not disclosed as yet and until now there are no approved diagnostic procedures for a great number of drug reactions. Medications are capable to cause the development of all types of immunopathologic reactions, described by Gell and Coombs, but IgE-mediated and T lymphocytes mediated reactions are the most common of them Hyperproduction of IgE antibodies by antigen specific B lymphocytes underlies immediate allergic drug hypersensitivity reactions. Binding of specific IgE antibodies to highly affinic receptors on the surface of mast cells and basophils, their interaction with the drug antigen results in the release of preformed mediators (histamine, tryptase), tumor necrosis factor and newly formed mediators (leukotriens, prostaglandins, kinins, cytokines). These mediators can be used as diagnostic biomarkers of drug

hypersensitivity. Clinically these reactions manifest with urticaria, angioedema, rhinitis, conjunctivitis, bronchspasm, gastrointestinal disorders or anaphylaxia, anaphylactic shock. Their development may be observed in application of foreign sera, beta-lactam antibiotics, sulphanilamides, analgizing agents, NSAIDs. The second type of drug allergic reactions is cytotoxic. In this type of reaction IgG or IgM interacts with the antigen fixed to the cell membranes, causing their damage mediated by a complement. Clinically it mainly manifests with immunopathological reactions of blood cells, e.g. immune hemolytic anemia. The emergence of some clinical forms of drug allergy may be caused by immune comlex reactions (type III, according to Gell and Coombs classification system). The basis of them is formation of immune complexes, their deposition in the vascular bed on the endothelial membranes of the small-calibre vessels with the consequent tissue damage and microcirculation disorders. Immune complex reactions run with the involvement of a compliment into the pathological process, and anaphylotoxins C3a and C5a produced in this process cause histamine, proteolytic enzymes and vasoactive amines to be released from the mast cells and basophils. This mechanism is the leading one in the development of serum sickness, vasculitis, systemic lupus erythematosus, Arthus phenomenon, some exanthemas of drug origin. The most frequent reason of immune complex variant of drug allergy is application of antibiotics, sera, vaccines, sulphanilamides, anesthetics, NSAIDs, new immunobiologic preparations (based on monoclonal antibodies). However, in recent years special attention has been drawn to delayed allergic reactions to medications, which are mediated by T lymphocytes. The most common target for T lymphocytes responding to medications is skin, but other organs may also be involved in the process. First, processing of drug antigen by dendrite cells if performed, then antigen is transported to the regional lymph nodes, where it is presented by T cells. Later antigen-specific T lymocytes migrate to the targeted organ, and after antigen exposure they are activated and secrete proinflammatory cytokines, which cause inflammation and damage of the tissue. Clinically delayed drug hypersensitivity reactions manifest with dermatologic symptoms: itching maculopapulous rash, fixed drug rashes, vasculitis, toxic epidermal necrolysis, Stevens–Johnson syndrome, generalized bullous fixed drug rashes, acute generalized exanthematous pustulosis and symmetric drug-related intertrigous exanthemas, located on extensor surfaces of the limbs. Internal organs can also be affected by the pathological process (isolated or in combination with dermatologic symptoms resulting in hepatitis, kidney damage, hypersensitivity pneumonitis, cytopenia. It has been also noted, that one and the same patient can develop several types of immunologic reactions to pharmacological preparations. Thus, it is proved, that both IgE-mediated and cell-mediated reactions participate in the development of allergy to insulin. Numerous medications and/or their metabolites are haptens, but binding to proteins, they form full antigen. Such newly

formed antigens can induce both IgE and T cell-mediated drug hypersensitivity reactions. Of great interest are current investigations, demonstrating obvious relation of genetic factors with the risk of developing immediate and delayed allergic drug reactions. It is testified, in particular, by the revealed interrelations between the Stevens Johnson syndrome, epidermal toxic necrolysis, induced by carbamazepine and HLA-B*1502, and also by association of IL-4 and IL-10 gene polymorphisms with immediate drug hypersensitivity reactions to beta-lactam antibiotics. Viral infections, including herpesviruses, as have been estimated in recent years, can provoke drug hypersensitivity reaction and skin rashes, if a drug (usually antibiotics) is used in the period of infectious process. Clinical manifestations may be rather serious — in the form of DRESS-syndrome and other systemic manifestations. Hypersensitivity reactions to medications occur more commonly in patients, including children, suffering from allergic diseases. It is likely to be connected with the changes of metabolic body functions in biotransformation of medicinal compounds and, in particular, with changes in their acetylation activity, formation of antigen determinants while interacting with the body proteins.

Clinical manifestations of drug hypersensitivity

As shown above, clinical manifestations of drug hypersensitivity can be immediate and delayed relative to the time of starting the medication. Additionally, systemic (anaphylaxia, drug fever, serum sickness) and organospecific variants of drug allergic reactions are distinguished. In current publications, skin is considered to be the main target organ in drug hypersensitivity, though other organs can be involved in the pathological process: hemopoiesis system (eosinophilia, cytopenia, hemolytic anemia), respiratory system (rhinitis, bronchospasm, laryngeal edema, pulmonary eosinophilic infiltrate), urinary system (glomerulonephritis, nephritic syndrome, interstitial nephritis), hepatobilliar system (hepatocellular lesions, cholestasis). The main syndromes characteristic of drug hypersensitivity, including those described recently, are considered below.

Skin lesions in drug allergy. Dermatologic symptoms are the most frequent in drug allergy, due to a high immune activity of the skin. Rashes are of polymorphic character. They are accompanied by itching, which is most intensive in measles-like or scarlatiniform rash. Maculopapulous rash. Papulous and/or measles- like rash compose 75–90% of drug-induced skin eruptions. The onset of rash is observed, as a rule, 1 week after medication exposure. They are not usually dangerous, if there are no other manifestations. Cytotoxic CD4+ T cells are the prevailing type of cells in this case. However, progression of eruptions to more serious manifestations, including toxic epidermal necrolisis, which is mainly mediated by CD8+ cytotoxic T cells, is possible. These cutaneous changes mostly disappear some days after the preparation is discontinued, which is often accompanied by peeling of epidermis, leaving areas of

discoloration. The main difficulty of clinical diagnosis of these pathological conditions is to differentiate them from infectious exanthems. Some clinical variants of drug hypersensitivity are realized in a certain combination of infectious agents and medications. An example is the risk of exanthema occurrence in using antibacterial preparations of aminopenicillin group in patients with infection, caused by Epstein–Barr virus. Urticaria. It is considered at present as a rather typical variant of drug rashes, but it occurs not so often as maculopapulous rash. Urticaria presents itching blisters of various size and localization, completely disappearing during 24 (48) h, sometimes associated with Quincke's edema. Blisters usually appear relatively quickly — from several minutes to several hours after starting the preparation, may be a component of anaphylactic reactions, includinf fatal ones. In some patients drug urticaria is based on IgE-mediated allergic reactions. Though in the majority of cases of drug hypersensitivity pseudoallergic urticaria variants are observed, which may be caused by NSAIDs, angiotensin converting enzyme inhibitors and other medications. In individuals, suffering from chronic urticaria, allergy to NSAIDs is noted in 30% of cases. Angioedema of drug etiology is clinically characterized by rapid development in the area of lips, eyelids, sometimes auricle, a dorsal surface of the hands and feet, and in the region of genitals. Fixed dermatitis is an interesting type of drug rash, consisting of one or several elements (erymatous, bullous, in the form of plates), of various shapes and sizes, with distiguished boundaries. They are established to occur in one and the same place each time the preparation is introduced. Discontinuance of the medicine is usually accompanied by reduction of symptoms but often with retained hyperpigmentation, which allows easy determination of the affected area. If the drug is introduced a second time, symptoms recur within 2 h, the number of elements often increases. This clinical variant is usually associated with CD8+ T cells. When the area of skin involvement is not large, the course is likely to be favorable, but in the extensive process with the systemic symptoms in the form of fever and arthralgia the prognosis may be not so optimistic and differential diagnosis includes Stevens–Johnson syndrome. Acute generalized exanthematous pustulosis (AGEP) is one of the most serious forms of drug allergy described in recent years. This pathologic condition often comprises acute fever (over 38°C) and skin eruptions in the form of small pustules within the areas of erythema arising within several hours after starting the causative medication. Mucous membranes may be involved in the process in 25% of cases, but the course may remain favorable enough. Characteristic for this condition are neutrophilosis, moderate eosiniphilia. In some cases edema of the face and arms is observed, but in general inner organs are rarely affected. The pharmaceuticals usually causing AGEP syndrome include beta-lactams, NSAIDs, chinolones, macrolides, calcium channel blockers, and also antimalarial drugs, such as chloroquine. No evident genetic markers associated with AGEP have been found. Drug-induced

hypersensitivity syndrome (DHS or DiHS) and DRESS-syndrome. These syndromes represent reactions to medications, accompanied by eosinophilia and systemic symptoms potentially threatening the life. They were first described not long ago, when anticonvulsunt preparations were used. Clinical characteristics include acute onset, rash, fever, and at least one of the syndromes (lymphadenitis, hepatitis, nephritis, pneumonia, thyroiditis) in combination with hematologic impairments (eosinophilia, atypical lymphocytes, thrombocytopenia, leucopenia). However, rash may not be always present, its character may be significantly different in various patients. Mortality rate may reach 10%, more often from hepatic insufficiency. Usualy symptoms appear 2–6 weeks after starting the offending medication, which is an important diagnostic criterion. Symptoms may last for weeks and months after the causative agent is discarded. The most common preparations associated with DRESS/ DiHS are found to be carbamazepine and other aromatic anticonvulsants, sulphanilamides, allopurinol, a number of drugs against HIV. The mechanism of syndrome development is referred to reactions of IVb type. An important role in the development of this syndrome is given to reactivation of herpesvirus 6, and other herpesvirus infections (Epstein–Barr virus, cytomegalovirus, herpesvirus 7). Exudative erythema multiforme ischaracterized by polymorphic eruptions in the form of erythema, targe-shaped papules, which can progress to vesiculous and bullous lesions and form erosions at their sites. Eruptions are mainly distributed acrally: on the hands, feet, upper and lower limbs. Mucous membranes may also be affected. Erythema multiforme is a polyetiological disease, with underlying reactions of hypersensitivity to drugs or infections, but in some cases it is associated with other pathological conditions, e.g. Kawasaki disease. Treatment of the patients is based on stopping the offending drugs or treating the existing infectious illnesses. In some cases treatment is recurrent due to unremoved antigen stimulation. Stivens–Johnson syndrome is considered by many specialists as a heavy form of exudative erythema multiforme, in which a large skin area is involved in the pathological process presenting polymorphic eruptions including formation of bulls, ulcerations, lesions of mucous membranes, visceral organs, fever, marked malaise. Other investigators consider this syndrome as an independent disease close in its genesis to the syndrome of toxic epidermal necrolysis. Both syndromes are thought to be the forms of abnormal necrotic reactions of the skin and mucous membranes to medicaments and/or infections, accompanied by epidermis and epithelium detachment. Historically they were classified as forms of exudative erythema multiforme, but at present they are considered as different diseases. Toxic epidermal necrolysis is a heavy variant of drug allergy running with bulleous skin damage, mortality rate reaching 30%. Some authors regard Stevens–Johnson syndrome as its milder form. The differences are in the area of skin lesions and in the character of cutaneous alterations. The onset is noted to have a sudden rise of

temperature, malaise with subsequent eruptions, which are painful to touch. Then blisters start forming, a classic Nikolsky's sign appears, when a slight lateral pressure results in epidermis rejection. Histologically it corresponds to keratinocyte apaptose with separation between the derma and epidermis. Mucous membranes of the mouth and reproductive organs are being involved in the process as well as that of intestine and eyes, leading sometimes to blindness. These reactions are immune-mediated and HLA-associations with certain medications are described. Skin manifestations are mainly caused by cytotoxic T cells but other cells can play an important role in ithe formation of this syndrome. Granulysin, tumor necrosis factor and some other molecules play a special role among the basic molecules, which mediate toxic damage of keratinocytes both in this syndrome and Stevens-Johnson syndrome. Their identification is used as diagnostic tests, when managing patients with these diseases. In addition to the skin lesion variants, described above, other skin reactions to the drugs are possible: photodermatitis — erymatous eruptions on the open body parts, formation of vesicles, bulls is also possible; Arthus–Sakharov phenomenon — local allergic reaction in the form of infiltrate, abscess; erythema nodosum — hypodermic nodes of the red color, localizing mainly on the anterior surface of both shins, may be followed by subfibrility, malaise, arthralgias and myalgias; allergic vasculitis — symmetric eruptions, leaving long-term pigmentation, localizing usually in the lower third of the shins, ankles, buttocks; contact allergic dermatitis — appearance of erythema and edema at the site of medication exposure, vesicles and bulls are also possible.

Systemic and organ damages in drug allergy

As indicated above, despite the fact, that the skin is the major target organ in drug allergy, other organs can also be involved in the pathologic process, and systemic effects are possible as well. Anaphilaxia is a serious, life-threatening, generalized or systemic reaction of hypersensitivity. Conditions with a similar clinical picture, called nonallergic anaphlaxia, may occur in clinical practice. Anaphylactic shock refers to the heaviest life-threatening manifestations of anaphylaxia to the allergen contact (medication), followed by marked hemodynamic disorders resulting in circulation insufficiency and hypoxia of all vital organs. High lethality rate has been noted. Serum sickness is an acute allergic reaction developing according to immune complex mechanism as a response to the introduction of heterologous sera, beta-lactam antibiotics, sulphanilamides, cytostatics, NSAIDs, monoclonal antibodies. Symptoms appear 1–3 weeks after drug exposure as eruptions (urticaria, maculopapular rash), fever, arthralgia (mainly of the large joints), lymphodenopathy. Disease duration is from several days to several weeks depending on its severity. Drug-induced fever may be provoked by application of beta-lactam antibiotics or other antimicrobial agents and have manifestations as in drug allergy. It is characterized by a rise of body temperature from subfebrile values to 39°C, may last for a short or long time. The mechanism of its

development is immune complex or cell mediated. In contrast to other fevers, the patient feels rather well. The fever subsides 2–3 days after the offending medication is discontinued. If the preparation is administered a second time, it recurs several hours later.

Manifestations of drug allergic reactions in children

The majority of allergic reactions to drugs in children are connected with administration of beta-lactam antibiotics, NSAIDs occupy the second place, and then in the decreasing order are macrolide antibiotics, sulphanilamides, anticonvulsant drugs, radiocontrast substances, chemiotherapy preparations and other medications. The risk factors of forming drug allergy in children are acute respiratory viral infections, especially in those predisposed to allergy, herpesvirus infections. Atopia, bronchial asthma, urticaria, atopic dermatitis are significant risk factors for formation of children drug allergy. The main difficulty in its diagnosis is differentiation of papuar/measles like rash with possible viral exanthemas, which are very often observed in this age group. Differential diagnosis is frequently very complicated, it is necessary to estimate the temporal relationship between drug intake and the reaction onset; it is important to consider the condition of the skin, mucous membranes, presence of fever, lymphodenopathy, changes in laboratory tests (eosinophilia of the peripheral blood, increase of hepatic transaminases level). In the current literature it is recognized, that the main clinical manifestations of drug hypersensitivity in children are diverse skin rashes and urticaria. Other manifestations are mentioned not so often: allergic rhinitis, angioedema, attacks of bronchial asthma, stomatitis, hemorrhagic vasculitis, enteritis, fever, anaphylactic shock, Stevens–Johnson syndrome, Lyell's syndrome. Predominant symptoms of drug hypersensitivity in children with bronchial asthma, atopic dermatitis or dermato-respiratory syndrome are diverse. In children with bronchial asthma the most common manifestations of drug allergy are bronchial asthma attacks (35.6%), the second place is given to urticaria (28.6%); in 19.5% of children allergy manifests with various exanthemas, in 11.7% of patients in the form of angioedema. In children suffering from atopic dermatitis drug allergy manifests often with exacerbation of atopic dermatitis (44.8%), urticaria and angioedema, occurring with equal incidence, take the second place (10%), exanthemas are noted in 16.8% of patients with this disease. In children with combined manifestation of skin and respiratory allergy drug hypersensitivity reactions most commonly manifest with acute atopic dermatitis (37.5%), angioedema (22.5%), rarer with bronchial asthma attacks (17.5%) and urticaria (15.6%).

Current approaches to drug allergy diagnosis

The existing scientific data do not allow formation of comprehensive complex of measures on diagnosing drug allergy. In this connection, methods of general clinical diagnosis continue to be of determining value, especially history-taking (allergologic,

pharmacologic and family history), general clinical examination with revealing the main syndromes typical of drug allergy. To diagnose some clinical and pathogenetic variants of drug allergy, in vivo testing and some biological in vitro testing can be performed. However, the list of certified methods of drug allergy investigation available for practical use is rather scanty. The majority of methods remained within the frames of study projects. Thoroughly performed history-taking is of principale importance in the diagnosis of drug allergy. The list of questions may be considered classic: to establish the sequence of symptom occurrence, their duration and connection with the intake of medications to which hypersensitivity reactions seem to develop; to determine the time interval between the onset of the reaction and the last dose of the drug, the influence of treatment discontinuance on symptom dynamics, as wll as the results of using in the past other medicines of the same class. Of great importance are data on allergic reactions and diseases in the patient's relatives, including reactions to medications. Allergologic and pharmacologic history gives grounds to suspect in a patient the development of drug allergy or its rejection with a great deal of confidence. It should be taken into consideration, that 1–10% of people with drug allergy have a syndrome of multiple drug intolerance (intolerance to three and more drugs, which are not connected either structurally or pharmacologically). As to the instrumental and laboratory methods of investigation in drug allergy, it is underlined in the majority of the current published reports, that their choice is determined by the specificity of clinical manifestations, intensity of systemic and organ specific symptoms, the supposed mechanism of drug hypersensitivity reaction. In this connection, hemogram, radiological lung examination, investigation of hepatic and renal functions, determining antinuclear and anticytoplasmatic antibodies, specific immunological tests, and in some cases tissue biopsy are included in the list of diagnostic methods. Thorough clinical examination of patients with drug hypersensitivity allows evaluation of the character, severity and danger of symptoms and conduction of the adequate laboratory study. Such approach helps in the majority of cases to make a correct diagnosis. In the acute phase of hypersensitivity reaction it facilitates to make a decision to stop or continue the treatment, which might have provoked formation of drug hypersensitivity reaction. If there exists the danger of patient's condition worsening, the suspected drugs should be discarded. Identification of offending antigen and biomarkers typical of certain hypersensitivity reaction are of substantial help in diagnosis of drug allergy course additionally to medical history and clinical data. Over the last years intensive studies are being carried on in this direction. Allergological diagnosis can be conducted using in vivo and in vitro methods.

In vivo methods (skin tests, provoking tests) are usually economically affordable and clinically informative. However, these tests can be performed only 4–6 weeks after stopping drug hypersensitivity reaction, and require observation of special

conditions. This reduces their value as they cannot be applied for emergency diagnosis and therapy (post-factum diagnosis). When it is impossible to exclude the diagnosis of drug allergy on the basis of medical history and clinical data, specific allergological diagnosis should be carried out in specialized centers. It will assist in establishing a diagnosis and recommending alternative pharmacotherapy. Allergological diagnosis (skin, provocation) can be performed after gathering allergological and pharmachological history. Allergo logical examination is often required to confirm allergic nature of drug hypersensitivity reactions relative to antibiotics, NSAIDs, and anesthetics. Skin tests. Skin testing is an available method for hypersensitivity reaction diagnosis. However, information about the development of standard diagnostic allergens on the basis of medications has not been found (at least in Russia). Prick testing and intradermal tests are especially important to identify IgE related mechanisms of drug allergy. Prick-tests are recommended for primary screening examination. Intradermal testing can be performed in case of negative prick test findings, they are informative enough in case of immediate hypersensitivity reactions to beta-lactam antibiotics, heparin, and sometimes in delayed reactions as well. To determine the possibility of T cell-mediated drug hypersensitivity delayed reactions, patch testing (application skin tests) and/or intradermal tests are performed. In some cases negative results of skin testing can be explained by the fact, that it is not the medication but its metabolites possess immunogenic properties. In such situations drug provoking tests can be used to confirm the diagnosis. Drug provocation test is the golden standard for identification of the drug having caused the development of hypersensitivity reactions. Provocation tests with a drug which is supposed to cause the side-effect can confirm or exclude the diagnosis of drug hypersensitivity reaction. Such tests can be done as early as 1 month after the primary drug allergic reaction by a specially trained personnel in specialized centers having an experience in early identification of hypersensitivity reactions, and capable of rendering an adequate aid in case of life-threatening conditions . Contraindication to provocation tests is availability of life-threatening drug hypersensitivity reaction (anaphylactic shock, other systemic reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, vasculitis). The route of introducing the suspected medication in provocation tests is mainly the same as in its initial application. But preference is given to peroral route, as it is connected with a lower risk of drug hypersensitivity reaction development.

Biological in vitro tests. The development of biological methods of diagnosing drug hypersensitivity reactions is believed to be a very promising direction. Such methods are advantageous for the patients receiving multi-drug therapy and in heavy hypersensitivity reactions, when in vivo tests with medications are contraindicated. This kind of examinations is safe for the patient and is possible to be performed at the

peak of clinical manifestations. Among in vitro tests the majority of methods implemented into clinical practice are based on measurement of allergen-specific IgE antibodies to drug allergens. However, drug hypersensitivity IgE-related reactions seem to be less common than delayed hypersensitivity reactions (T lymphocytes-mediated). Besides, commercial kits for identifying specific IgE are available for a limited number of medications including amoxicillin, ampicillin, cephaclor, penicillin, insulin (bovine, porcine, human), adrenocorticotropic hormone, suxamethonium and some other preparations. Absence of specific IgE to the examined medications (negative test results) does not mean that immediate-type of drug allergy may be completely rejected in this case. Determination of the level of IgE or IgG specific to medicaments may be justified in cases of medication induced cytopenia, hypersensitivity reactions to vaccines or dextrans. The sensitivity of these tests remains unexplored, and they are seldom used in diagnosic purposes. Among other (not IgE) in vitro diagnostic methods the following tests for detection of mediators, released from various effector cells involved in the pathogenesis of drug hypersensitivity are used: identifying cystenyl leukotriens, produced in vitro by isolated peripheral blood leukocytes after stimulation by drug allergen; determining the level of histamine, tryptase, granzyme in blood serum, released from basophils and mast cells in acute drug allergic reactions, including anaphylaxia; detecting cytokines released by lymphocytes. At present, the possibility of drug hypersensitivity diagnosis using methods based on the cells participating in the immune response, is being studied. Examples of these methods are given below. fluorometric Test for release of histamine from basophils with measurement is supposed to be rather promising and is now studied for revealing hypersensitivity reactions to certain drugs. Basophil activation test is also one of the tests used for diagnosis of drug allergy. Basophils with high affinity of their receptors to IgE are used in this test as indicator cells. Basophils, activated by allergens in the presence of allergen-specific IgE, express markers of activation, such as CD63 and CD203c, and intracellular markers on their membranes. Such alterations in basophils can be detected by flow cytometry method using specific monoclonal antibodies to activation markers. Donor’s basophils, patient’s serum with a supposed drug allergy and a causative antigen are used in this diagnostic procedure. Reactions of lymphocyte blast-transformation with various drug allergens and some other methods are also being used for diagnostic purposes. Immunologic laboratory methods, listed above, such as test for release of histamine from basophils (under the influence of the diagnosed medication), basophil activation test, cysteine leukotrienes release test, lymphocyte activation test, reactions of lymphocyte blast-transformation may be in some separate cases rather useful, but at present they are not used in routine clinical practice, as they are not standardized for drug allergy diagnosis [93]. Informativity of many of them has not been convincingly proved and further

investigations require substantial financial expenditure. It should be underlined, that to confirm or exclude completely presence of hypersensitivity to various medications using only in vitro tests is impossible today. Test results must be interpreted in combination with medical history and clinical examination data. The last achievements in the field of genetics revealed a number of HLA-allels, connected with forming hypersensitivity drug reactions, affecting mainly the skin. For example, the associations found between hypersensitivity to abacavir and HLA-B*57:01 and between carbamazepine-induced Stevens–Johnson syndrome and HLA-B*15:02 are realized in clinical practice — test-systems are developed for identification of susceptible people, which help to prevent drug allergy to carbamazepines restricting their application.

Conclusion

Hypersensitivity immune reactions to medications, according to the present concepts, are divided into immediate reactions (within 1–6 h after starting the preparation manifesting with various forms — from mild to life-threatening symptoms of anaphylaxia), or delayed reactions (several hours to several days after the offending medication is started, manifesting clinically with exanthemas in the majority of cases). Specific diagnosis of drug allergy is performed using in vivo tests (prick tests, intradermal tests, patch tests, provocation tests) and in vitro test (identification of drug specific IgE test, basophil activation tests, leukocyte blast-transformation reactions, quantitative identification of cytokines and other proteins, e.g. granzyme and tryptase in the peripheral blood). However, at present not all these methods are accessible in real clinical practice, the list of commercial kits for drug allergy diagnosis is limited. It is especially important in patient managing to rely on history-taking and general clinical examination data, to consider the available information on association of drug allergy and infections by viruses of herpes group, especially in children population, on hereditary predisposition to forming some kinds of drug allergy.

Study Funding and Conflicts of Interest. The work was not supported by any sources and there is no conflicts of interest related to it.

References

1. Meliqulov, O. J., & Ernazarova, M. S. (2022). DORI VOSITALARINING BARQARORLIGINI OSHIRISH YO'LLARI. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(Special Issue 4-2), 978-982.
2. Meliqulov, O. J., & Kodirov, N. D. (2022). 1.4-BENZODIAZEPINNING TIBBIYOTDA QO'LLANADIGAN VOSITALARI. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(8), 313-317.
3. Meliqulov, O. J., & Baymuradov, E. S. (2022). VITAMIN B12 NING OLINISHI VA UNING AHAMIYATI. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(8), 324-327.

4. Меликулов, О. Ж., Кодиров, Н. Д., & Баймурадов, Э. С. (2022). ИСПОЛЬЗОВАНИЕ БАРБАРИСА В ФАРМАКОТЕРАПИИ. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(Special Issue 4-2), 911-913.
5. Mirzoyeva, F. A., Imamova, Y. A., & Meliqulov, O. J. (2022). MEDICINAL PLANTS AND THEIR PROPERTIES. *Web of Scientist: International Scientific Research Journal*, *3*(4), 1140-1144.
6. Meliqulov, O.J., & Baymuradov, E.S. (2022). VITAMIN B12 NING OLINISHI VA UNING AHAMIYATI. Oriental renaissance: Innovative, educational, natural and social sciences, 2 (8), 324-327.
7. Эрназарова, М. Ш., & Бахромова, Б. З. (2022). Исследования свойств лекарственных растений содержащих алкалоид. *Science and Education*, *3*(11), 106-116.
8. Нажмитдинов, Х. Б., Олимов, С. М., & Бахромова, Б. З. (2022). ПОЛЕЗНЫЕ СВОЙСТВА ФРУКТА–ПЕРСИК. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(9), 327-332.
9. Baxromova, B. Z., & Ernazarova, M. S. (2022). Dorivor lavanda o'simligi haqida umumiy ma'lumot va uning tibbiyotda qo'llanilishi. *Science and Education*, *3*(11), 88-95.
10. Shernazarovna, E. M., & Zokirovna, B. B. (2023). KAMQONLIK SABABLARI VA UNI TABIIY YO'L BILAN DAVOLASH CHORALARI. *ОБРАЗОВАНИЕ НАУКА И ИННОВАЦИОННЫЕ ИДЕИ В МИРЕ*, *15*(1), 160-165.
11. Shernazarovna, E. M., Zokirovna, B. B., & Shuxrat o'g'li, D. B. (2023). RAYHON O'SIMLIGIGA UMUMIY TAVSIF. *ОБРАЗОВАНИЕ НАУКА И ИННОВАЦИОННЫЕ ИДЕИ В МИРЕ*, *15*(1), 166-168.
12. Shernazarovna, E. M., & Zokirovna, B. B. (2023). YALPIZ (MENTHA) O'SIMLIGINING DORIVOR XUSUSIYATLARI. *ОБРАЗОВАНИЕ НАУКА И ИННОВАЦИОННЫЕ ИДЕИ В МИРЕ*, *15*(1), 169-172.
13. Olimov, S. M., & Baxromova, B. Z. (2022). ZANJABIL HAQIDA UMUMIY MA'LUMOT. TIBBIYOTDA QO'LLANILISHI. *Journal of new century innovations*, *14*(1), 156-160.
14. Shernazarovna, E. M., & Zokirovna, B. B. (2023). QANDLI DIABET KASALLIGI VA UNING ASORATLARI. *Journal of new century innovations*, *26*(4), 116-121.
15. Бахрамова, Б. З., Эрназарова, М. Ш., & Муминбоев, Д. Ж. (2023). ОТНОШЕНИЕ ЧЕЛОВЕКА К ПРИРОДЕ И ОТНОШЕНИЕ ПРИРОДЫ К ЧЕЛОВЕКУ. *ББК 30.16 Б 63*, 89.

16. Bakhromova, B., & Mo'minboyev, D. (2023). THE LIFE OF ABU ALI IBN SINA AND HIS CONTRIBUTION TO THE FIELD OF PHARMACY. *Бюллетень педагогов нового Узбекистана*, *1*(9), 39-42.
17. Baxramova, B., & Mo'minboyev, D. (2023). SHIFOBAXSH ZANJABILNING TIBBIYOTDA QO'LLANILISHI. *Центральноазиатский журнал образования и инноваций*, *2*(9), 86-89.
18. Baxramova, B., Xolbo'tayeva, K., & Mo'minboyev, D. (2023). BIOLOGIK FAOL MODDALARNING INSON SALOMATLIGIGA TA'SIRI. *Инновационные исследования в науке*, *2*(9), 5-8.
19. Zokirovna, B. B., & Khusan, K. (2023). VALERIAN ROOT IN THE TREATMENT OF SLEEP PROBLEMS AND RELATED DISORDERS-A SYSTEMATIC REVIEW AND METAANALYSIS. *Journal of Modern Educational Achievements*, *10*(1), 21-27.
20. Бахрамова, Б., & Муминбоев, Д. (2023, September). ОТНОШЕНИЕ ЧЕЛОВЕКА К ПРИРОДЕ И ОТНОШЕНИЕ ПРИРОДЫ К ЧЕЛОВЕКУ. In *Международная конференция академических наук* (Vol. 2, No. 9, pp. 9-13).
21. Yuldashev, S., Halimbetov, Y., Usmanova, M., Naimova, Z. S., & Khamraeva, M. (2021). National Processes In Uzbekistan And The Formation Of The Internationalist Maturity Of The Younger Generation. *The American Journal of Medical Sciences and Pharmaceutical Research*, *3*(06), 167-175.
22. .Хасанова, Г. Р., & Усмонова, М. Б. (2022). Применение фасоли (phascolus) в медицине. *Science and Education*, *3*(11), 117-125.
23. Sh, A., Kuylieva, M. U., & Usmanova, M. B. (2022). Application of phytotherapy in the treatment of chronic prostatitis. *Web of Scientist: International Scientific Research Journal*, *3*(5), 466-470.
24. Sh, A., Kuylieva, M. U., & Usmanova, M. B. (2022). Application of phytotherapy in the treatment of chronic prostatitis. *Web of Scientist: International Scientific Research Journal*, *3*(5), 466-470.
25. Имамова, Ю. А., & Усманова, М. Б. (2022). РОДИОЛЫ РОЗОВАЯ ДЛЯ ПОВЫШЕНИЯ РАБОТОСПОСОБНОСТИ ОРГАНИЗМА. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(Special Issue 4-2), 901-904.
26. .Имамова, Ю. А., Усманова, М. Б., & РОДИОЛЫ, Р. ORIENSS. 2022. № Special Issue 4-2. *URL: https://cyberleninka. ru/article/n/rodioly-rozovaya-dlya-povysheniyarabotosposobnosti-organizma*.
27. Усманова, М. Б., & Имамова, Ю. А. (2022). ЛУК РЕПЧАТЫЙ–ПРИМЕНЕНИЕ В МЕДИЦИНЕ. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(Special Issue 4-2), 914-917.

28. Қўйлиева МУ, Э. М., Усмонова, М., & Имамова, Ю. (2021). General information on the age of Chilonjtyda, its composition, application in folk medicine, its features and their different types, conditions for cultivation. *Шкурова, Д., Усманова, М., & Имамова, Ю*.
29. Usmanova, M., & Toshpolatov, C. Endokrine gland system, humoral managementof the organizm. *Researchjet journal of analisis and inventions In Voiume*, *1*.
30. Шкурова, Д., Усманова, М., & Имамова, Ю. (2021). Private technology of powders Preparation of powders with abrasives, dyes and hard powders, extracts and essential oils. *Экономика и социум,(11), 90*.
31. Usmanova, M., & Yuldoshev, C. Importanse of lipids in the cell, simple and compleks lipids, classification. Researchjet journal of analisis and inventions.
32. Imomova, Y., Usmonova, M. B., Yo'Ldoshev, S., & Ahmadov, J. (2021). DORI VOSITALARINING ZAMONAVIY TAHLIL USULLARI. *Oriental renaissance: Innovative, educational, natural and social sciences*, *1*(8), 587-596.
33. Усманова, М., Эрназарова, М., Куйлиева, М., & Хасанова, Г. (2021). Дорихона фаолиятини ташкил этиш, дорилар саклаш чора тадбирлари. *Экономика и социум,(11)*, *90*(6).
34. Хасанова, Г. Р., Усманова, М. Б., & Нажмитдинов, Х. Б. (2022). ВИТАМИНГА БОЙ ЛОВИЯ (PHASCOLUS) ЎСИМЛИГИНИНГ УМУМИЙ ХУСУСИЯТЛАРИ. *Oriental renaissance: Innovative, educational, natural and social sciences*, *2*(9), 333-336.
35. Xasanova, G. R., Ernazarova, M. E., & SHIFOBASH, Q. O. T. F. J. ORIENSS. 2022. № Special Issue 4-2. URL: https://cyberleninka. ru/article/n/shifobash-qoqi-otining-foydali-jihatlari.
36. Yakubova, Sarvinoz Raxmonqulovna, & Xasanova, Gulbaxor Raxmatullayevna (2022). KAMQONLIK HAQIDA TUSHUNCHA. Oriental renaissance: Innovative, educational, natural and social sciences, (Special Issue 4-2), 897-900.
37. Mirzoyeva, F. A., Imamova, Y. A., & Meliqulov, O. J. (2022). Medicinal plants and their properties. *Web of Scientist: International Scientific Research Journal*, *3*(4), 1140-1144.
38. Usmanova, M. B. (2022). Geksikon shamchasini tayorlashda uning asosni almashtirish. *Science and Education*, *3*(11), 213-220