Ministry of Health of Ukraine
Poltava State Medical University

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Minutes № from
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METHODOLOGICAL RECOMMENDATIONS FOR CONDUCTING AND PREPARING FOR PRACTICAL CLASSES

Academic discipline	Clinical immunology and allergology
*Module **4***	Clinical immunology and allergology
Content module	Clinical immunology and allergology
*Topic **№11***	Drug allergy. Emergency conditions in allergology
Course	5
Hours	2

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Methodological recommendations for the practical training for independent work of students in preparation for the practical training and during the class were prepared by:
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Methodological recommendations were re-approved at the meeting of the Department of Internal Medicine of Internal Medicine №3 with Phthisiology_____
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1. Relevance of the topic.

In their practice, physicians of any speciality face adverse drug reactions and complications of drug therapy. Given the fact that in recent years the number of new drugs and their abuse, both in self-medication and in conditions of iatrogeny and polypharmacy, has been increasing, the increase in cases of adverse drug reactions is understandable.

Drug allergy is one of the types of adverse drug reactions that requires timely diagnosis, differential diagnosis with other complications and appropriate therapy, sometimes urgent.

The physician should know the etiology, mechanisms of development of allergic reactions and pseudoallergic reactions to drugs, as this knowledge will prevent the occurrence of reactions, and if they are present, will help timely diagnosis and therapy, as well as preventive measures aimed at preventing such reactions in the future.

Specific objectives:

1. To determine the degree of risk of developing drug allergy based on allergic history.
2. To diagnose and differentiate drug allergy from other complications of drug therapy based on clinical and anamnestic data.
3. Make a plan for the examination of patients with drug allergy (or risk groups) using immunological and allergological methods.
4. To prescribe emergency therapy in case of severe reactions to drugs, to carry out prevention aimed at the absence of allergic and pseudoallergic reactions to drugs.

Theoretical questions for practical training:

1. What factors influence the increase in the incidence of drug therapy complications?
2. Give a classification of adverse drug reactions.
3. What are the mechanisms of allergic reactions to drugs? Give examples of manifestations of drug allergy that develops by the mechanism of immediate type reaction?
4. Give examples of drug allergy that occurs by the cytotoxic type. What drugs are most often used to develop this type of reaction?
5. Immunocomplex reactions to drugs: nosology, mechanism of development, drugs that cause the development of allergy by this mechanism.
6. Delayed hypersensitivity reactions: nosology, mechanism of development, drugs that cause the development of allergy by this mechanism.
7. Mechanisms of development and clinical manifestations of pseudo-allergic reactions to drugs.
8. Principles of diagnosis of drug allergy based on clinical and anamnestic criteria.
9. Principles of laboratory diagnosis of drug allergy: allergological and immunological methods used.

10. In vivo diagnostic tests: features of use, indications and contraindications.
11. In vitro diagnostic tests: advantages and disadvantages.
12. Criteria for the differential diagnosis of allergic and pseudoallergic reactions to drugs.
13. Principles of drug therapy.
14. Principles of therapy of pseudoallergic reactions to drugs.

Орієнтовна основа дії

Indicative basis of action

The term "drug allergy" refers to complications of drug therapy associated with immune system disorders and occurring according to the mechanisms of allergic reactions. Drug allergy can be caused by reactions of humoral and cellular types. It can occur to the administration of any drug, but the mechanisms of drug hypersensitivity development are different.

In recent years, due to the success of pharmacology and the creation of a large number of medicines, their use and abuse has been steadily increasing. The number of undesirable effects of drug therapy is also growing accordingly.

Until the 1990s, the nomenclature of medicines used in the United States was 26,000 items, in Germany - 5,000, in England - 55,000, in France and Greece - 25,000, in Spain - 15,000, and in the USSR - 5,000 medicines. Today, the number of medicines has increased significantly.

Among the factors that support the high level of medication complications are the following:

1. Increased use of medicines by the population;
2. Widespread self-medication as a result of the possibility of purchasing medicines without prescriptions;
3. Insufficient or delayed medical information on side effects of medicines;
4. Polypharmacy and polytherapy;
5. Environmental pollution by industrial waste;
6. The use (sometimes unjustified) of a large number of medicines, vaccines and serums;
7. Diseases of infectious, parasitic, viral or other nature, which are not allergic themselves, but due to their pathogenetic features, there is a possibility of allergy (production of antibodies to any antigens, including drugs) Example: allergic reactions to penicillin often occur in patients with athlete's foot; allergy to drugs occurs during long-term therapy of chronic infections (staphylococcal or streptococcal);
8. The use of antibiotics, vitamins and other drugs used in the treatment and feeding of livestock, which provides an opportunity for sensitisation of the population due to impurities in food products (milk, meat) obtained from these animals.

Numerous observations and studies have pointed to a large number of mechanisms for the development of drug reactions, most of which remain

unknown, insufficiently studied and debated.
This explains the complexity of the problem of drug therapy complications and their classification.

Prevalence of drug allergy
The prevalence of drug allergy, according to researchers, varies widely, from 1 to 30% or more, but these data require serious analysis, as they do not take into account the presence and prevalence of placebo reactions.
Among the medicines that cause allergic reactions, most researchers name penicillin: up to 55%, other antibiotics - from 0.8 to 18%, sulfonamide drugs - from 0.5 to 10%, NSAIDs - up to 25%, local anaesthetics - up to 6%, and other groups.
The frequency of penicillin allergy, according to Russian researchers, ranges from 0.7 to 10%, of which anaphylactic shock is recorded in 0.002% of cases. Severe allergic reactions to most β-lactam antibiotics have also been reported.
In clinical practice, the presence of cross-reacting properties between drugs with a β-lactam ring in their structure (penicillins, cephalosporins) is important. It is known that 2-8% of patients with penicillin allergy may be allergic to cephalosporin. The appendices contain a list of medicines to which cross-allergic reactions occur.

Classification of adverse drug reactions

The existing classifications of adverse drug reactions are most often based on the pathogenetic principle.

The most practical for a physician is the following version of the working classification of side effects that develop when using medicines:

1. Pharmacological side effect

2. Toxic side effects: overdose; toxic reactions in case of excretory functions disorders; toxic reactions from drug accumulation, from increased drug absorption, from enzyme inhibition, toxic pharmacological side effects (enzymopathies, toxic reactions caused by genetic diseases); toxic reactions caused by incorrect administration of drugs.

3. Adverse reactions caused by immune system disorders:

allergic reactions, which occur by mechanisms of immediate and delayed hypersensitivity; cytotoxic and immunocomplex reactions, which can lead to the development of allergic and autoimmune diseases.

4. Pseudoallergic reactions to medications.

5. Carcinogenic effect of medicines.

6. Teratogenic effect of drugs.

7. Mutagenic effect of drugs.

8. Drug dependence: substance abuse, withdrawal symptoms, psychological dependence.

9. Effect of drugs on microbial ecology: dysbiosis, candidemia, resistance.

10. Effect of drugs on the main metabolic processes in the body.

11. Adverse reactions and complications caused by drug interactions:

in the body, chemical and pharmacological incompatibility.

12. Adverse reactions and complications of mixed genesis.

13. Side effects of medicines caused by environmental factors.

Among all the complications, we will focus on allergic and pseudo-allergic reactions to drugs.

Types of allergic reactions.

Type I. Immediate hypersensitivity reactions (reagin type, anaphylactic reactions). It is known that this type of allergy is caused by hyperproduction of total Ig E and production of specific Ig E antibodies, and their subsequent fixation on basophils and mast cells, and atopic diseases develop. The most common clinical manifestations of this type of allergy are urticaria, rhinitis, Quincke's edema, atopic dermatitis, bronchial asthma, and anaphylactic shock. It is these diseases or their exacerbations that manifest allergic reactions to drugs.

Most often, immediate hypersensitivity reactions occur to the use of serums, penicillin, sulfonamides, non-steroidal anti-inflammatory drugs, vitamins, and theophylline drugs.

Reactions and diseases of this type are called atopic.

Type II. Cytotoxic reactions.

Ig G and Ig M antibodies are fixed to the patient's own cell, which has become a target under the influence of drugs, and then this cell is altered by activation of complement, macrophages or killer cells. This reaction is best studied in cytopenias. Blood cells under the influence of drugs become antigens and are destroyed by the above mechanism. It should be noted that there are several pathways leading to cell alteration:

1. hapten mechanism - the drug combines with a blood cell

2. immunocomplex mechanism - a drug (or metabolite) acts as an antigen, or a conjugate: a drug combined with a part of plasma. Subsequently, antibodies are produced to this antigen and the created immune complex is fixed to the cell.

3. 3. The cell changed under the influence of the drug is the antigen.

In all these pathways, as mentioned earlier, cytopenic reactions, both acute and chronic, develop. This type of reaction can also occur under the influence of antibiotics, primarily penicillin, sulfonamides, and haemolytic anaemia can occur under the influence of alpha-methyldopa.

Type III. Immunocomplex reactions.

These reactions are caused by precipitation of immune complexes with complement activation. This type is associated with the deposition of immune complexes created in the vessels on the cell membranes of the vascular endothelium with their subsequent damage, as well as in the synovial fluid and endothelium of the renal glomeruli. As with type II, Ig G and M play a role in these reactions, and the complement system is subsequently triggered. The most common manifestations of this type of drug reaction are: serum sickness, Artyusu's phenomenon, vasculitis, glomerulonephritis, allergic arthritis. This type of reaction can be caused by penicillins and other antibiotics, serums, vaccines, sulfonamides, anaesthetics, etc.

Type IV. Cell-mediated reactions (delayed hypersensitivity).

Type I helper T-lymphocytes and macrophages play the main role in these reactions. It is type I helper T cells that secrete cytokines: γ-IFN, IL-2 and TNF, lead to the formation of allergic inflammation. This type of reaction includes contact sensitisation, exanthem and drug fever. This type of reaction can be caused by sulphonamide drugs, alkaloids, metal preparations (gold, mercury), penicillin and some other antibiotics, local anaesthetics, antiseptics, etc.

Combined sensitisation

In some cases, different types of reactions occur simultaneously. For example, a combination of haemolytic manifestations with an erythematous skin rash that develops into an exanthema. Such heterogeneity can be observed in allergy to penicillin, insulin and other drugs.

Autoimmune mechanisms

Medications can cause autoimmune diseases. Examples include SLE-like manifestations after the use of novocainamide and apresin, and SLE-like syndrome can be observed after the use of furadonin. Autoimmune mechanisms may be involved in the development of tubular and interstitial nephritis, haemorrhagic alveolitis, chronic aggressive hepatitis, and pseudolupus.

Below is a clinical classification of allergic reactions to medicines, as almost all organs and systems can be affected by allergies.

Clinical classification of allergic reactions to drugs.

I. Systemic reactions

1. Anaphylactic shock.
2. Vasculitis.
3. Serum disease.
4. Drug fever.
5. Autoimmune diseases induced by the medicinal product.
6. Complex multisystem reactions.

II. Organ reactions

1.Skin reactions:

a) urticaria and angioedema;

b) vasculitis;

c) fixed drug rash;

d) toxic epidermal necrolysis (Lyell's syndrome);

e) Stevenson-Johnson syndrome;

f) erythema multiforme;

h) exfoliative dermatitis;

h) erythroderma;

i) contact dermatitis;

k) photo allergic reactions;

l) maculopapular exanthema.

2.Hematological reactions.

3.Lesions:

a) kidneys;

b) liver

c) lungs;

d) heart.

Pseudo-allergy to drugs.

Pseudoallergic and anaphylactoid reactions occur due to the direct release of histamine and other mediators from mast cells and basophils, which occurs without the formation of specific Ig E antibodies or the formation of an antigen-antibody complex on the mast cell/basophil membrane. These reactions can occur in patients who have not had previous contact with the drug, as there is no sensitisation in pseudoallergy. There are several mechanisms for the development of pseudoallergy to drugs, which are associated with:

1. Histamine mechanism, caused by an increase in histamine concentration:

a) due to the release of large amounts of histamine from mast cells and basophils, i.e. histamine liberation (e.g. muscle relaxants, narcotic analgesics, radiopaque agents, plasma substitutes, antibiotics, etc;)

b) in case of violation of its inactivation (for example, in case of long-term use of anti-tuberculosis drugs, analgesics, antibacterial drugs)

c) in case of ingestion of histamine and other amines with food and medicines;

d) increased production of histidine, phenylalanine, tyrosine by intestinal microflora with decarboxylating activity, for example, in case of dysbiosis.

This type of pseudoallergy is often called pseudoatopic.

2. Activation of the complement system by the alternative pathway with the formation of anaphylatoxins CzA and C5a, activation of mast cells and release of histamine (e.g. radiopaque agents, dextrans).

3. Disturbance of fatty acid metabolism, including arachidonic acid with excessive formation of leukotrienes (e.g., NSAIDs).

4. Formation of bradykinin (angiotensin-converting enzyme inhibitors).

A large number of substances related to histamine liberators have been described. Most of them are non-immune in nature, some are immune (they are listed in the Appendix).

Different types of allergic and pseudoallergic reactions can occur to the same drug.

Principles of diagnosis and differential diagnosis of drug allergy.

Taking into account the previously reviewed material, it becomes clear that, first of all, it is necessary to determine whether this complication is allergic or pseudoallergic, or whether it is another reaction, and secondly, to identify the causally significant allergen and establish a diagnosis.

It should be noted that the issues of diagnosis and differential diagnosis of drug therapy are very complex and, despite the availability of a large number of tests both in vivo and in vitro, there is no single method that would allow a doctor to establish an etiological diagnosis reliably and without any danger to the patient. Therefore, the most important thing is to take a thorough history. The doctor should remember that if the patient has had any reaction to a drug, do not prescribe this drug, drugs of this group and other groups with cross-antigens (listed in the appendix) in the future. Diagnosis is even more difficult in the case of polypharmacy.

Pitsky V.I. and co-authors cite the following patterns in the diagnosis of drug allergy:

1. An allergic reaction to a drug can occur only if the patient is sensitised to that drug or a drug with cross-antigenic properties. Several days (5-7) should pass between the first and the second encounter with the drug. However, it is possible that a person is unaware of previous sensitisation (e.g. by drinking milk from cows that have received penicillin).

2. An allergic reaction does not depend on the dose of the drug and can occur at doses much lower than therapeutic ones.

3. Allergic reactions to medicines resemble "classic" allergy symptoms in terms of clinical manifestations

4. After discontinuation of the drug that caused the allergy, in most cases, the reaction develops rapidly.

Laboratory methods for diagnosing drug allergy.

As mentioned earlier, in the diagnosis of drug allergy, in vivo diagnostic methods (skin and provocative tests) and in vitro diagnostic methods (basophil degranulation test, leukocyte blast transformation test, lymphocyte migration inhibition test, determination of specific Ig E antibodies to drugs and in vitro basophil cell stimulation test) are used.

Skin diagnostic tests. Since drug allergy is dose-independent, skin tests may pose a threat to the health of patients with drug allergy. Cases of anaphylactic reactions to intradermal tests with penicillin and other antibiotics have been described. On the other hand, if a person encounters a medicine for the first time during a skin test, he or she will not have a reaction, but this does not mean that an allergy cannot develop upon repeated contact, as the first encounter is sensitising. Thus, many authors believe that conducting skin tests for medications for all patients is dangerous and inappropriate. Skin tests help in the diagnosis of drug allergy and are appropriate in the following circumstances

1. if the drug cannot be replaced with another, equally effective drug, and there has been a history of a reaction while being treated with this drug in combination with others;

2. if the patient has had prolonged professional contact with the drug required for his/her treatment;

3. if a patient with an allergic disease needs to be prescribed a highly allergenic drug that he/she has received previously;

4. in case of vital indications for penicillin administration to patients with fungal skin lesions.

Contraindications to skin tests for medicines, as well as skin tests in general, are:

1. The presence of an unconditional allergic reaction to the drug, including anaphylactic shock.

2. Acute period of any disease.

3. Uncompensated heart disease, kidney disease, thyrotoxicosis, pregnancy, severe diabetes mellitus.

It should be recalled that skin tests differ depending on the type and degree of hypersensitivity. For the diagnosis of type I reactions, drip, scratch and intradermal tests are used. We remind you that since many drugs are haptens, a negative skin test does not exclude the presence of an allergy to the complex formed in the body. Also, the possibility of a general, sometimes severe reaction is not excluded, so the doctor should have all the drugs used in the treatment of anaphylactic shock. To diagnose type IV reactions, an application skin test is used, which is informative and practically safe.

Provocative tests.

They are used only in specialised medical institutions if necessary. They include sublingual, nasal and inhalation tests. If a reaction occurs, the drug is eliminated and the necessary medications are used. The most commonly used test is sublingual, and very rarely in patients with allergic rhinitis and asthma - nasal and inhalation tests.

Basophil degranulation test (Shelley test).

The use of this test, as well as the test of histamine release by sensitised leukocytes, the mast cell degranulation test, is assessed differently. But on average, the correlation between the clinic and the test is no more than 50%.

Leukocyte blast transformation test.

This test is based on the lymphocyte blast transformation reaction (LBTR) when exposed to mitogens or allergens. According to many researchers, the level of information content of this test is also no more than 50%.

Determination of specific Ig E antibodies to drugs.

This test is easy to use and has no contraindications on the part of patients, as it is performed in vitro. The essence of this method is the interaction of allergens with specific Ig E antibodies to them, the formation of a complex, its subsequent labelling

with a reagent and the determination of colour, the intensity of which is proportional to the concentration of specific Ig E. The advantage of this method (which includes the radioallergosorbent test-RAST and MAST-multiple allergosorbent test) is the ability to examine patients simultaneously with a large number of allergens, and the availability of results within 6-24 hours. This test demonstrates a high correlation with clinical manifestations, high sensitivity and objectivity of the results. The disadvantage is the rather high cost.

According to many researchers, allergen-specific diagnostics by determining specific Ig E antibodies is justified when skin samples are not available or limited.

There are also new tests that have been developed relatively recently and are not yet widely used. One of these tests is CAST (basophil antigen stimulation test in vitro). The essence of this method is to determine the level of sulfoleukotrienes synthesised de novo, or to determine the CD 63 marker of basophils, the expression of which increases after the addition of a drug (allergen) to a suspension of patient's leukocytes. The advantages of the method are: high specificity, the ability to determine the degree of individual patient reactivity, and lower cost compared to the determination of specific Ig E.

TASKS FOR SELF-CONTROL

1. A 22-year-old patient was delivered to the emergency department of the emergency room, who, after tooth extraction, developed swelling on the face and within 2 hours spread to the neck, chest, and upper extremities. The edema was pale and dense. The condition did not improve after the paramedic administered Dimedrol and No-Spa. Possible causes of edema development:

a) immediate allergic reaction

b) delayed allergic reaction

c) arachidonic acid metabolism disorder

d) deficiency of C 1 inhibitor

e) reduction of histaminopexy

The correct answer is: d

2. In the context of ARI, a patient receiving a sulfonylamide drug, a non-steroidal anti-inflammatory drug, acidified drinks and crying developed a patchy papular rash on the skin, accompanied by itching, and difficulty breathing. The following mechanisms of reaction development are possible, in addition to:

a) type I allergic reaction

b) type II allergic reactions

c) histamine variant of pseudo-allergy

d) pseudo-allergy caused by fatty acid metabolism disorders

e) pseudoallergic reaction caused by excessive activation of the complement system

The correct answer is b

3. A patient receiving a sulfonamide drug, a non-steroidal anti-inflammatory drug, acidified drinks and crying developed a patchy papular rash on the skin, accompanied by itching and shortness of breath. Therapy should include all of the following except:

a) cancellation of all prescribed medications

b) antihistamines

c) enterosorbents

d) bronchodilators

e) specific immunotherapy

The correct answer is e)

4.The student was referred to the therapeutic department after deterioration of the condition, while taking medications for the treatment of acute bronchitis: antibiotic therapy (gentamicin), antihistamine (diazoline), mucolytic (bromhexine). The condition is severe. Blood count: leukocytes 0.6 x 10 /l, eosinophils 80% and

monocytes -20%. The diagnosis of leukaemia is excluded. Mechanism of the disease development:

a) type I allergic reaction

b) type II allergic reaction

c) type IV allergic reaction

d) pseudoallergy histamine variant

e) pseudo-allergy caused by a violation of fatty acid metabolism

The correct answer is b)

5. The student was referred to the therapeutic department after deterioration of the condition, while taking medications for the treatment of acute bronchitis: antibiotic therapy (gentamicin), antihistamine (diazoline), mucolytic (bromhexine). The condition is severe. Blood count: leukocytes 0.6 x 10 /l, eosinophils 80% and monocytes -20%. The diagnosis of leukaemia is excluded. To confirm the diagnosis, the following should be used:

a) skin tests

b) provocative tests

c) determination of the level of serum IL-4

d) determination of the HLA phenotype

e) determination of the titre of cytotoxic antibodies: Ig G and Ig M

The correct answer is e)

6. During an X-ray contrast examination with the use of an iodine-containing drug, the patient lost consciousness, blood pressure dropped to 90/60 mmHg, heart rate-120 beats/min. Possible causes of this condition:

a) anaphylactoid shock caused by histamine mechanism

b) type II allergic reaction

c) psychogenic reaction

d) delayed type hypersensitivity

e) pseudoallergic reaction caused by a violation of fatty acid metabolism

The correct answer is a)

7. The patient has a history of Quincke's edema after administration of a penicillin antibiotic. If antimicrobial therapy is necessary, it is not recommended to prescribe the following group of drugs:

a) aminoglycosides

b) macrolides

c) cephalosporins

d) fluoroquinolones

e) sulfonamides

The correct answer is c.