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RESEARCH ARTICLE

NON-TARGET EFFECTS OF PHARMACOLOGICAL DRUGS

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ABSTRACT

The paper discusses the immunosuppressive effects of pharmacological drugs. The task is to reduce the possible side effect of drugs due to annually increasing public access to medicines as a result of a large number of OTC drugs available for sale accompanied by a lack of objective information about their possible negative consequences. Here, we present information on the study of immunosuppressive effects of various pharmacological groups and their impact on public health. To a certain extent, this information allows predicting the effect of drugs on the body's responsiveness, and their contribution to aggravation or elimination of initial immune disorders in patients.

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INTRODUCTION

The current stage of the clinical medicine development is characterized by a significant increase in the number of drug-induced lesions of various organs. The rising significance of this pathology's related to the liberalization of public access to medicines, the over-the-counter availability of a large number of OTC drugs for sale, and the widespread aggressive advertising in the absence of objective information about possible side effects (Emtsev, 2012; Zemskov et al., 2016).

Immunosuppressive effects of antibiotics: Many experimental studies and clinical observations have revealed immunosuppressive effects of even a short course therapy of antibiotics such as penicillin, streptomycin, tetracyclines, anti-tuberculous, and antifungal drugs (Khaitov, Ataullakhanov, 2012; Pokrovsky*et al*., 2013; Zemskov*et al*., 2013). The most noticeable effects of antibiotics are defects in forming the primary immune response and differentiation of stem cells, caused by levomycetin, rifampicin, doxycycline; weakening of vaccine immunity against bacteria and viruses with levomycetin and cephalosporins.

Other noted effects are decreased anti-infectious resistance against influenza virus, Pityriasis Rosea and Pityriasis Versicolor, etc., induced by aminoglycosides, penicillins, cephalosporins and suppression of cytotoxic activity of T-lymphocytes by amphotericin B, tetracycline, doxycycline, minocycline, lymecycline, cephalothin, and levomycetin. There are also descriptions of inhibition of chemotaxis, opsonization, and bactericidal activity of phagocytes by cephalosporins, aminoglycosides, tetracycline, erythromycin, tobramycin, amikacin, doxycycline, lymecycline, rifampicin and amphotericin B, and inhibited formation of immune memory cells, complement activity, lysozyme, β-lysines, bactericidal activity of blood serum with ampicillin. There are reports of postoperative infectious complications development in patients when treated with neomycin, oleandomycin, sinthomycin, streptomycin, etc. (Zemskov *et al.,* 1996, 1999). The basic chemical preparations for tuberculosis treatment: kanamycin, streptomycin and, to a lesser degree, rifampicin, Isoniazid, pyrazinamide, and ethionamide, especially combinations of Isoniazid + rifampicin + streptomycin and Isoniazid + rifampicin + kanamycin, in case of delayed use,

suppress the immune response to thymus-dependent and thymus-independent antigens, delayed-type hypersensitivity (DTH), and indicators of the body's nonspecific defense (Yushchuk *et al*., 2014). Currently, we can exclude almost completely the clinical use of polymyxin, levomycetin, vibromycin, despite the periodically observed sensitivity of some purulent-septic complications agents to these antibacterial drugs, as these drugs inhibit phagocytosis and aggravate the course of purulent-septic processes. However, the use of these drugs with target immunomodulators significantly reduces mortality in patients with generalized purulent infections (Zemskov *et al*., 2015).

Immunosuppressive effects of other drugs: Active immunosuppressors are reserpine, Phenamine, Furaginum, Furacilin, Phenibut, sodium alproate, and other psychotropic agents. Antihistamines inhibit natural anti-infective resistance, immunity, including the vaccinalone, "erase" the immune memory. Amidopyrine, Indomethacin, salicylates suppress the Ag-Ab response, which means that in all cases where antibodies are needed for protection (diphtheria, toxicosis, etc.), this response is poor. Sulfamethoxazole, Bactrim, and Nitrofurantoin inhibit the formation of antibodies, the functional activity of lymphocytes, whereas Paracetamol and Indomethacin reduce the phagocytic activity of peripheral neutrophils, immediate and delayed hypersensitivity. In case of prolonged use in therapeutic doses, salicylates, non-steroidal anti-inflammatory drugs, inhibit the immune responsiveness of the body, which led to being labeled as "minor immunosuppressants". They are known to suppress formation of antibodies against various viruses, bacteria and their toxins, heterologous proteins and erythrocytes, migration of T- and B-lymphocytes, disturb cooperative interactions of immunocytes, and inhibit the development of cell-mediated immune responses, as well as contribute to the development of medical secondary immunodeficiency (Borisov, 2005).

Immunostimulating effects of traditional drugs: Erythromycin has shown to stimulate the phagocytic immunity link, increase the bactericidal activity of leukocytes, their migration, and chemotaxis. Polyene antibiotics – Nystatin, Levorin, Nezoral, amphotericin B activate phagocytosis, the nonspecific resistance factors, functional activity of T- and B-lymphocytes, DTH, antiviral immunity, response to bacterial vaccines. Clindamycin, Lincomycin, Erythromycin, Ciprofloxacin, and Rifampicin promote the activation of neutrophilic leukocytes, which strengthens opsonization, chemotaxis, and phagocytosis (DK Novikov, PD Novikov, 2009).

Plant extracts of the Araliaceae, Umbelliferae, Euphorbiaceae, and Rosacea families also possess pronounced immunostimulating effect. Among representatives of the Araliaceae family, a high activity is recorded in eleutherococcus, ginseng, Aralia Manchu, Echinacea Purpurea, Rhodiola Rosea preparations. Polysaccharides from fungi, algae, lichens, and higher plants demonstrate immunostimulating, antitumor, radioprotective, hepatoprotective effects and antioxidant and antisclerotic activity. One of the mechanisms of plant polysaccharides action is their direct or indirect effect on macrophages or the complement system. Vitamins and vitamin-like compounds not only exhibit antioxidant activity (A, E, K), regulate bioenergetic processes (B1, B7, inosine, carnitine), enhance anabolic mechanisms (B6, B9, B12), but also show immunomodulating ability, especially when combined. Trace elements (metals) have a certain immuno-biological activity. Thus, zinc increases resistance to respiratory infections, stimulates antibodygenesis, DTH and, at the same time, causes thymic hypoplasia and the secondary immunodeficiencies development. Lithium has psychotropic and immunotropic activity, affects the levels of cyclic adenosine monophosphate, stimulates granulocytes and phagocytosis, whereas copper is a cofactor of enzymes and protects cell membranes, stimulates T-helpers. Selenium activates the functions of T-cytotoxic/suppressor lymphocytes, protects cell membranes from peroxidation; iron is an immune activator and potentiates the synthesis of DNA in cells, whereas beryllium and vanadium induce sensitization, modulation, stimulation of lympho-proliferation and suppression of phagocytosis and antibody formation (Zemskov *et al.*, 2011).

Side effects of drugs: The above immunotropic phenomena of drug therapy are the cause of induction or aggravation of the initial allergy, autoimmune reactions with the risk of turning the latter into autoaggressive diseases or formation and weighting of immunosuppressive conditions in patients (Briko *et al*., 2013). Negative effects of antibacterial drugs also include their excessively strong bactericidal action on microorganisms which, in presence of blood clots, leads to the release of endogenous activators of immune and autoimmune reactions (acute phase proteins, low-molecular nucleic acids, and endotoxins (Zemskov *et al*., 2013)). An addition to the list are the mutant effects of antibiotics. Thus, actinomycin D inhibits transcription of genetic information, Olivomycetin inhibits the RNA synthesis, rifamycin inhibits the RNA polymerase, whereas puromycin and tetracycline inhibit protein synthesis on ribosomes. In some cases, the immunosuppressive effect of antibiotics is very useful. For example, especially when violating the rules for the introduction of anti-infectious drugs (daily, course doses, modes of administration, etc.), microflora forms plasmid-induced antibacterial resistance, causing the secretion of enzymes which destroy or even convert medicines into food substrates. This ability is easily transferred to other microorganisms, regardless their species.

Serum disease: The disease develops when tetanus, anti-influenza, antidiphtheria and other sera, immunoglobulins, foreign hormones, vaccines, toxoids, etc. are introduced into the body. At the center of this pathology is the formation of immune complexes and their deposition on the walls of blood vessels, activating complement, the active factors of which cause clinical manifestations. With the first administration of drugs, symptoms appear on the 7^{th} – 15^{th} day; with repeated administration, the reaction can develop instantaneously or in a few days.

Clinical manifestations of serum disease: Skin polymorphic rashis a constant (90%) symptom of this pathology. Fever occurs 2 days before the rash or simultaneously, and is of permanent, intermittent or subfebrile nature. Articular syndrome occurs in the form of edema and hyperemia of the joints, synovitis, myalgia, respectively, along the nerve trunks; polyneuritis and lymphadenopathy are also observed. Patients develop edema of the face, scrotum and other skin areas, as well as hemorrhagic vasculitis, low blood pressure, arrhythmias, changes on an electrocardiogram, myocarditis, pericarditis, myocardial infarction, etc.

At an early stage, in the blood, leukocytosis can develop, and at the peak of the process - leukopenia with relative lymphocytosis and eosinophilia, thrombocytopenia, complement deficiency, decreased blood clotting, and hypoglycemia. The mild form is common and is accompanied by individual symptoms, itching rashes, swollen lymph nodes. The medium-heavy form is accompanied by a more emphasized clinical scenario with an almost constant lymphadenopathy, changes in the cardiovascular system. The heavy form is registered less often and is characterized by an acute onset with a high fever, generalized rash and shortness of breath.

Effect of traditional drugs on hemato-immune parameters of patients: Since the main parameters of the patient's immunograms depend on the values of the leukogram indicators, the analysis of the immune status should take into account data on the effects of traditional drugs on key laboratory tests (Tables 1 and 2).

Prevention of non-target immunotropic effects: For drugs, it is achieved if the following algorithm is observed (Zemskov *et al*., 2013; Briko, Pokrovsky, 2015): (1) the use of drugs strictly according to the indications, (2) the compliance with the rules of administration (optimal terms, doses), (3) the use of non-traditional methods of administration (aerosol, endolymphocytic, lymphotropic, intranasal, sublingual, etc.), (4) taking into account the patient's immune status, (5) implementation of alternative immunocorrection, (6) combination of long-term and massive courses of antibiotics with vaccinotherapy and immunomodulation. After antibiotic therapy, especially administrated orally, it is necessary to carry out an adequate correction of dysbiosis, deficiency of local intestinal immunity, systemic immune responsiveness; it is also desirable to combine it with pharmacological modulators (sodium nucleinate, etc.) or non-drug treatments such as low-intensity laser radiation, ozone therapy, etc.

Preliminary correction of immune disorders: To implement this approach, special computer software has been developed No. 2014619643 and No. 2015612811. Since the formation of immune disorders is closely related to other pathological processes in the body, to eliminate them, auxiliary therapy with traditional medicines has been developed: (1) To suppress nonspecific resistance, adaptogens should be administrated (ginseng, Chinese magnolia vine), as well as minor immunocorrectors (Apilac, Dibasol, prebiotics, probiotics, and synbiotics), (2) in patients with dysnucleotidosis, nucleic acid preparations (sodium nucleinate, Derinat, Ridostin), (3) in patients with dysbacteriosis eubiotics, enzymes. (4) To eliminate metabolic disorders, *(4a)* energizers (riboflavin, nicotinamide), *(4b)* activators of glycolysis and the tricarboxylic acids cycle (thiamin, riboxin, biotin, lipoate), *(4c)* stimulants of antioxidant protection (β-carotene, retinol, α-tocopherol, ascorbic acid, Hypoxenum, Limonar, coenzyme), *(4d)* hepatoprotectors (Essentiale, Karsil, Lipostabil, Phosphogliv, Tykveol, Betimil, Catergen, Flakozid, *(4e)* metabolic agents (potassium orotate, Hypoxenum, Tramelan, Pentoxyl, Methyluracil, Mildronate, nucleic acid preparations: sodium nucleinate, ridoxine, Derinat, polynucleotide, Poludane) are used. (5) In patients with infectious syndrome with immunodeficiency, it is preferable to use antibiotics with stimulating effects (see Table 1), and in the treatment of angina caused by β-hemolytic streptococcus type A, preferable are antibiotics of the penicillin series, simultaneously reducing antigenic load and suppressing autoimmune reactions, (6) in patients with pseudo-allergy, enteral sorbents are administered (Polyphepan, Polysorb, Enterosgel), antispasmodics (No-Spa), cholagogue preparations (Allochol), etc.

Drug-induced systemic lupus erythematosus (SLE): Long-term administration of many drugs can cause the appearance of LE cells, antibodies to DNA, clinical symptoms of SLE. Prolonged administration of Novocainamide, Apressin, Diphenine, Isoniazid, Thiouracil may contribute to the development of SLE symptoms. Less often are described the cases of SLE after administration of sulfonamides, penicillin, Aminazine, Butadione, Quinine, Griseofulvin, Methyldopa, Cyclophosphamide, Streptomycin, paraaminosalicylic acid, preparations of gold, sera and vaccines, large doses of immunostimulators (Khaitov *et al.*, 2000). The development mechanism of this form of SLE is unknown, but most likely it comes down to drugs, in combination with body proteins, transforming into autoantigens, as well as effects of drugs on the function of suppressor cells (most often the initial symptoms of drug SLE show up as rheumatic joint pain, especially in interphalangeal joints). Tropism to DNA is reliably shown in connection with Apressin (hydralazine) which, as a hapten, forms conjugates with nucleic acids, antibodies to which react with single-stranded (or denatured) DNA. Generally, antibodies do not bind complement (apparently, therefore, the kidneys are rarely affected in patients with drug-induced SLE). Continued drug administration is associated with increase in body temperature, unusual weakness, exudate in the joints, pleuritis, pericarditis, lymphadenopathy and splenomegaly, followed by cutaneous manifestations: "butterflies" (in contrast to idiopathic SLE, when a "butterfly" is a sign of the disease onset). Another difference between this form of SLE and the classical one is that the pathological process rarely affects the kidneys. As a rule, antibodies to native DNA are not determined, only to denatured DNA, as well as histones and lymphocytes. The prevalence in men and women is the same; note that with the with drawal of drugs, the symptoms disappear, and with the resumption of medication, they reoccur.

The following syndromes of drug-induced SLE are known. (1) The mixed connective tissue disease, manifested in seronegative SLE with rare kidney damage, the appearance of antibodies to RNA. It is characterized by arthritis, the Raynaud's syndrome, myositis, atherosclerosis, hand swelling. Occasionally, it is manifested as a combination of (a) "non-renal" SLE, (b) systemic sclerosis, (c) polymyosite, (2) the Provost syndrome, when a typical SLE develops without antinuclear factors, (3) Maas syndrome, when SLE is not associated with antinuclear factors and kidney disorders. The main symptom is polyarthritis in combination with polyserositis; antibodies to mitochondria are detected, (4) SLE-like manifestations can be observed with defects of the complement system (C1, C2, C4, C5, and C8 components). In this case, there is a decrease in the total complement level, but the level of antibodies to DNA does not decrease. The treatment of SLE can be divided into several stages, which are determined by the severity of the process. I stage. In mild cases, as well as in case of the cutaneous-articular variant of this disease, antimalarial drugs should be used in combination with non-steroidal anti-inflammatory drugs (NSAID) (in the US, primarily aspirin). IIstage. In case of kidney involvement in pathological process and in cases of severe systemic lesions, the use of high doses of glycocorticosteroids (GCS) is

Table 1. The effect of traditional medicines on the leukogram summands

Indicator	Change in parameter	Drugs
Leukocytes	Increase	Ampicillin, Allopurinol, adrenaline, atropine, corticotropin
	Decrease	Hydralazine, amidopyrine, amitriptyline, Aminazine, barbiturates, Bactrim, Butamide, haloperidol, dichlorothiazide, Isoniazid, indomethacin, chloramphenicol, lincomycin, metronidazole, oxacillin, rifampicin, streptomycin, tetracyclines, Phenacitin, quinine
Lymphocytes	Increase	Levodol, narcotic drugs, paraaminosalicylic acid
	Decrease	Phenitolin, corticosteroids, corticotropin
Neutrophils	Increase	Hydrocortisone
	Decrease	Aminazine, amitriptyline, Bactrim, Butamide, dichlorothiazide, Isoniazid, indomethacin, chloramphenicol, metronidazole, procainimid, rifampicin, chlorambucil
Granulocytes	Increase	Hydrocortisone
	Decrease	Clozapine, amidopyrine, anturane, Bactrim, phenylbutazole, haloperidol, gentamicin, Isoniazid, ibuprofen, procainamide
Eosinophils	Increase	Ampicillin, doxycillin, phenytoin, Isroniazid, carbenicillin, methyldopa, procainamide, nystatin, oleandomycin, digitalis, rifampicin, streptomycin, tetracycline, sulfonamides, phenothiazines, cephalosporins, erythromycin
	Decrease	Aspirin, indomethacin, corticosteroids, nicotinic acid, nicoinamide, epinephrine

Table 2. Immunotropic effects of non-immune drugs

Immunostimulatingeffect	**Immunosuppressive effect**
Antibiotics	*Antibiotics*
Erythromycin, amphotericin B, levorin	Neomycin, tetracycline, oleandomycin, streptomycin, penicillin, levomycetin
Nitrofurans	*Nitrofurans*
Furazolidone	Furacilin, Furaginum
Antiseptics	*Alkylating derivatives*
Chlorophyllipt, lysozyme	Cyclophosphan
Stimulants of metabolism	*Corticosteroids*
Potassium orotate, riboxin	Prednisolone, hydrocortisone, Metipred
Psychotropic drugs	*Antimetabolites*
Nootropil (piracetam), Phenamine. Sydnokarb	6-mercaptopurine, 6-fluorouracil
Plasma replacement solutions	*Psychotropic drugs*
Hemodez, reopolyglucin, gelatin	Sodium oxybutyrate, sodium alproate, Phenibut, reserpine, Aminazine
Anti-inflammatory drugs	*Anti-inflammatory drugs*
Reopyrin	Amidopyrine, salicylates
Enzymatic drugs	*Non-steroidal anti-inflammatory drugs*
Trypsin	Ibuprofen, indomethacin, voltaren
α-adrenomimetics	*Antihistamines*
Norepinephrine, mezaton	Dimedrol, suprastin, pipolfen
M-cholinomimetic agents	*Enzymatic drugs*
Carbacholin	Ribonuclease
β-adrenomimetic agents	*α-adrenoceptor blocking agents*
Dibasol	Phentolamine, tropafen, pirroksan
A, C, E, B group vitamins	*β-adrenolytic agents*
	Isadrin, isoproterenol

provided (1 mg/kg per day in prednisolone equivalent) or pulse therapy (15 mg/kg per day for 3 days). IIIstage. In this case, for the most severe symptoms, a combination of GCS, NSAID, and cytostatic (CS) agents is administrated. Preference is given to Cyclophosphamide, Azathioprine, Chlorobutin.

Metabolic effects of immunomodulating drugs: Almost all immunotropic drugs have a certain metabolic effect; probably, in a number of cases it is simply not studied. The metabolic effect of poly- and lipopolysaccharides manifests in the intensification of protein synthesis, the activation of the "adenylate cyclase– cyclic adenosine monophosphate" system, various enzyme systems, inclusion of ^{3}H-thymidine into the spleen cells. Experiments have shown the ability of levamisole to stimulate enzyme activity of the hexose monophosphate shunt, protein iodization in neutrophils, DNA synthesis, protein synthesis in lymphocytes and macrophages, increased secretion of α-glyconidase and cathepsin D in phagocytes, accumulation of intracellular cyclic guanosine monophosphate in peripheral lymphocytes and granulocytes, activation of receptors for IgG and C3 components of the complement on monocytes and macrophages. Muramyl dipeptide activates lysosomal enzymes, increases the intracellular cyclic adenosine monophosphate, prostaglandins, stimulates the DNA synthesis. Polyelectrolytes (polyacrylic acid and P-4-vinylpyrrolidone) promote the formation of DNA and RNA in vitro. Synthetic double-stranded RNA (poly I:C, poly A:U, and poly G:C) increase the inclusion of ^{3}H-thymidine in the lymphoid and other cells, stimulate the formation of adenylate cyclase, cyclic adenosine monophosphate. Methyluracil and Pentoxyl activate cholinesterase, formation of protein, nucleic acids in vitro. Thymus derivatives, myelopeptides, potentiate the synthesis of protein and nucleic acids in various cells. In addition, the former proved to be powerful regulators of lipid

metabolism, reduced blood glucose, normalized liver function (Zemskov *et al*., 2013).

Immunotropic effects of metabolic drugs: In various clinical models of diseases, namely, exacerbation of deep pyoderma, chronic pyelonephritis, their combination with urolithiasis, purulent infection of soft tissues with allergic dermatitis, true eczema, acute form and exacerbation of chronic salpingo-oophoritis, bacterial vaginosis, herpetic keratitis and urogenital chlamydiosis, it has shown the ability of antioxidant, metabolic drugs, food additives (hypoxene, tsygapan, limonar, tykveol), metabolic agents of nucleic origin (sodium nucleinate, Derinat, Isoprinosine, etc.) to correct the immune system disorders. The same is noted for non-specific inflammatory lung diseases (mixed, exogenous and endogenous bronchial asthma, chronic obstructive pulmonary disease, and their combinations), and other pathological processes. Note that this correction occurs at the level of the main populations and functional subpopulations of lymphocytes, natural killers, immunoglobulins of various classes, aggressive medium-mass molecules, circulating immune complexes, absorbing and metabolic ability of phagocytes, pro-and anti-inflammatory cytokines (Zemskov*et al.*, 2015, 2016, 2017).

Conclusion

It is shown that a large number of drugs (narcotic, sedative, steroidal and non-steroidal anti-inflammatory drugs, antibiotics, sulfonamides, and other) affect to some extent the responsiveness, contributing to the aggravation or elimination of initial immune disorders in patients, cause disorders in parenchymal organs, primarily, the liver, the kidneys, various parts of the hematopoietic and immune systems. It is generally implied that most broad-spectrum antibiotics, antihistamine, anti-inflammatory, narcotic, analgesic and other drugs inhibit, whereas metabolic and antioxidant agents, vitamins, adaptogens, plasma-substituting solutions, some psychotropic drugs stimulate the immune system. At the same time, low doses of drugs, as a rule, activate immune responses, whereas large doses inhibit them. However, this pharmacological "dose-effect" axiom depends not only on the concentration of the drug administered, but also the state of detoxifying, excretory and other body systems, the nature of nutrition, the state of the initial immune responsiveness, and other factors.

It should be also noted that the realization of these effects largely depends on the therapeutic support of the patient. Thus, amidopyrine increases the activity of many modulators, Brufen, that of Methyluracil, Obzidan, that of polysaccharide stimulants, a combination of antihistamine and antibacterial drugs summarize the suppressor properties, whereas sodium nucleinate reduces therapeutic doses of antibiotics and toxicity of drugs; corticosteroids stimulate the effects of bronchodilators, immunosuppressors, cardiac glycosides, indomethacin, suppress the effectiveness of vaccines, anti-diabetic, antihypertensive, narcotic, anticoagulant and other drugs; cytostatic agents have suppressor activity on immunostimulators, etc.

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