PharmacologyOnLine
Archives • 2021 • vol.2 • 978-983

POTENTIAL RISKS OF ANTIALERGIC DRUGS

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Abstract

Among more than 10 thousand diseases, according to the classification of ICD-11, allergies (from greek *allos* - other and *ergon* - action) are a very common disease of civilization: in the world more than 20% of the population suffer from allergies, that is, one in five people. Despite some advances in the pharmacovigilance system (official observations of drug safety), adverse reactions of antiallergic drugs still remain one of the reasons for paradoxical situations in pharmacotherapy, especially with their unsustainable use. In this article, the authors drew the attention of pharmacologists, doctors and pharmacists to the potential risks of antiallergic drugs and the rational conditions for their warnings.

Keywords: *alergia, antialergic drugs, side effect.*

Among more than 10 thousand diseases, according to the classification of ICD-11, allergies (from greek allos - other and ergon - action) are a very common disease of civilization: in the world more than 20% of the population suffer from allergies, that is, one in five people [27, 13].

The cause of allergy can be any substance of the environment [26, 25, 14], including almost all drugs that are in the ATC classification. All of them are incomplete antigens – haptens that irreversibly bind to tissue proteins and can cause sensitization of the body [12]. As a result of this connection, there are reactions of the delayed (after 2-3 or more days: systemic lupus erythematosus, rheumatism, etc.) and immediate type (after a few minutes: urticaria, anaphylactic shock, etc.) [20].

During these reactions, allergy mediators (histamine, bradykinin, cytokines, etc.) are released, which cause bronchospasm, a decrease in blood pressure, edema, itching, pain and dysfunction of many organs, including until the appearance of life-threatening anaphylactic shock, angioedema and serum sickness [24, 21, 19].

For the prevention and treatment of allergic diseases, more than 100 INN (International Nonproprietary Names for Pharmaceutical Substances) and several hundred of their brands have been created. These are blockers of H1 – histamine receptors (I, II and III generations), membrane stabilizers and anti-mediators, glucocorticosteroids and selective antagonists of leukotriene receptors [4]. This classification of antiallergic drugs and their activity is associated with the effect on various links in the pathogenesis of allergy. All antiallergic drugs have a membrane stabilizing and antiallergic effect, and some of them also have anti-inflammatory, antipruritic, sedative and other effects that eliminate the clinical manifestations of allergy [11, 12]. Among all existing antiallergic drugs, there is not one that would not have side effects (SE) from the central nervous system or cardiovascular and respiratory systems, gastrointestinal tract, blood system or other organs. [1]. Currently, antiallergic drugs occupy one of the leading positions among drug poisoning [3].

Blockers of H1-histamine receptor are widely used group of drugs for allergies that are included in many drug combinations for the treatment of colds, acute respiratory viral infection (ARVI) and other diseases [2]. The mechanism of SE of drugs in this group is not yet entirely clear [1]. They are known to interfere with the synthesis and activity of many mediator systems of the central nervous system. H1-histamine blockers, in addition to blocking H1-receptors, also cause antiserotonin and anticholinergic effects, increase dopamine activity, inhibit mast cell phosphodiesterase, reduce cytokine production and the formation of free radicals [4]. The M-anticholinergic activity of antiallergic drugs (especially diphenhydramine, chloropyramine) is a mechanism for the development of dryness of the mucous membrane of the digestive tract and respiratory tract, changes in the rheological properties of sputum, thickening and impaired evacuation. The selective action of H1 receptor antagonists is mainly associated not with central, but with peripheral H1 histamine receptors; in addition, they are structurally similar to antidepressants, which explains the mechanisms of their many not only therapeutic effects, but also SE [4].

Therefore, for the prevention and pharmacocorrection of SE of antiallergic drugs, doctor and pharmacist need to analyze the mechanisms of the possible SE of these drugs, the conditions that contribute to the appearance and measures to prevent them. Considering the danger of certain SE of antiallergic drugs for the health and life of the patient, the main thing in the pharmacotherapy of allergies is the preventive measures, especially those SE that can aggravate the disease or disrupt the functions of vital organs and systems of the body. In particular, of all antiallergic drugs the most dangerous in terms of cardiotoxicity are blockers of H1-histamine and serotonin receptors, as well as fenspiride and clarinase. Life-threatening ventricular arrhythmias develop when loratadine is combined with macrolides, quinidine, itraconazole, fluconazole, ketoconazole [1].

Depending on the value of blood pressure and the patient's pulse, one must be able to make an effective and safe choice of these drugs. Arterial hypertension and SE are characteristic of loratadine, promethazine, diphenhydramine, clemastine and clarinase, while other antiallergic drugs can cause arterial hypotension and tachycardia: loratadine, diphenhydramine, clemastine, fenspiride, clarinase

[26, 14, 24, 4, 1, 6]. Care should be taken to prescribe quifenadine, clemastine and clarinase to patients with severe cardiovascular diseases [4]. Children are more sensitive to the activity of antiallergic drugs. Children who take more than 10 mg (1 tablet) of terfenadine orally per day, there is a possibility of prolongation of the Q-T interval, ventricular arrhythmias, and even death [3]. With the simultaneous use of clarinase with sympathomimetics and MAO inhibitors, hypertension is possible up to a hypertensive crisis, and with digitalis preparations and terfenadine, the activity of ectopic foci of heart automatism increases [4, 30]. In the literature, dangerous cardiac arrhythmias are described when the antifungal drug ketoconazole is used together with terfenadine or astemizole [3]. Promethazine while blocking α-AR can cause orthostatic hypotension.

In recent years there has been a significant increase in the uncontrolled use of antihistamines by adolescents, especially in connection with their versatile action, since, in addition to the main antiallergic activity, they also have sedative and hypnotic effects, enhance the activity of analgesics and reduce body temperature [4, 1].

SE at the pharmacotherapy of antiallergic drugs that are associated with depression of the central nervous system take the second place in the total set of SE of antiallergic drugs [4, 1, 8]. In this undesirable effect of antiallergic drugs, their similar tendency remains as for blood vessels. First, most anti-allergic drugs inhibit many functions of the central nervous system. Those are sleep disturbance, dizziness, weakening of attention, slowing down responses are caused by the majority of H1 blockers – histamine and serotonin receptors, membrane stabilizers, selective antagonists of leukotriene D4 receptors and combined antiallergic drugs [18]. Significantly fewer drugs of this group cause excitation of the central nervous system (promethazine, diphenhydramine, clemastine, dimensionhydrinate, fenspiride, clarinase), headache, convulsions (oxatomide, loratadine) [1].

SE of H1 blockers – histamine receptors on the part of the central nervous system are mainly associated with their effect on the cholinergic receptors of the brain (anticholinergic) [1]. If long-term use of H1 blockers – histamine and serotonin receptors is necessary, preference is given to drugs of the II and III generations or alternates with drugs of the I generation every 5 days. Antihistamines of the II generation selectively act on the H1-histamine receptors, therefore they have less neurotoxicity and sedative effect. In addition, these drugs in therapeutic doses do not penetrate the blood-brain barrier and do not cause tachyphylaxis. The simultaneous use of cyproheptadine with tricyclic antidepressants can enhance the M-anticholinergic effect and the inhibitory effect on the central nervous system [1]. Quifenadine does not have a depressant effect on the central nervous system [1]. The pathological basis of parkinsonism (extrapyramidal disorders) of promethazine is associated with its neurotoxicity, in particular through the mechanism of activation of oxidative stress by free radicals in oxidation reactions [4]. Chloropyramine can be combined with caffeine or phenamine, but when used together with hypnotics or sedatives, then the central depressive effect is enhanced [8]. Ketotifen should be used with caution by persons whose work requires concentration. Due to SE, antihistamines (dizziness, mental retardation, general weakness, drowsiness) should not be taken while working [6, 10]. Mebhydrolin - the reference "daytime" antihistamine of the 1st generation, unlike diphenhydramine and chloropyramine, do not have a hypnotic effect, therefore it is used in patients who do not want to depress the central nervous system (operators, drivers) [4]. Clemastine is more active than diphenhydramine and lasts longer (8-12 hours), and also has less effect on the central nervous system [1].

Paradoxical SE for some drugs in this group of drugs are allergic reactions (azelastine, loratadine, promethazine, montelukast sodium, clarinase), angioedema (oxatamide, dimensionhydrinate, zafirlukast), anaphylactic reactions (oxatamide, clemastine) [10]. Therefore, acute allergic conditions are contraindicated for the appointment of oxatamide, and bronchospasm and attacks of bronchial asthma for the appointment of oxatamide, clemastine [29, 1, 11]. The administration of diphenhydramine during breastfeeding may cause paradoxical stimulation of the central nervous system in infants. In addition, this drug, as well as promethazine and chloropyramine, have a teratogenic effect on the fetus and can cause withdrawal symptoms in newborns. Usage of anti-

allergic drugs (diphenhydramine, chlorpyramine, clemastine) by women during pregnancy (the first 12 weeks) in order to prevent nausea and vomiting; there were observed congenital deformities (defects of the heart muscle and feet, an increase in the number of fingers) [1]. Therefore, when treating young children with mebhydroline, it is necessary to strictly adhere to the dosage recommendations (possibly psychomotor agitation) and should be taken only in case of urgent clinical need [1, 15]. Blockers of histamine receptors in significant quantities penetrate into milk, and therefore a contraindication for many antiallergic drugs are pregnancy and breastfeeding [1].

Children and the elderly are more sensitive to antihistamines [11]. Acute allergic conditions are contraindicated for taking oxatamide, and bronchospasm and acute attack of bronchial asthma for oxatamide, clemastine and selective antagonists of leukotriene D4 receptors (zafirlukast and montelukast) [21]. When prescribing oxatomide to patients with bronchial asthma, one should not abruptly change its dose, especially when combining therapy with glucocorticosteroids. If it is necessary to treat patients with liver damage, oxatomide should be prescribed, this drug should be used with half the usual dose, and always keeping the interval of administration. In case of anaphylactic shock or other acute and severe allergic reactions, therapy should be started with intravenous administration of chloropyramine, then switch to its intramuscular injections [1]. Montelukast sodium is not used to relieve acute asthmatic attacks, nor is it a substitute for inhaled bronchodilators [28, 22].

Glucocorticosteroids are the most effective anti-allergic drugs, but their intake is limited by numerous SE [1]. The dose of glucocorticosteroids used simultaneously with montelukast sodium should be gradually reduced under strict supervision. [22, 28]. During the treatment of allergic conditions with hydrocortisone or prednisolone, a diet with a limited sodium content is necessary to normalize the water-electrolyte balance. Glucocorticosteroids should not be abruptly canceled when replacing them with an antihistamine, since adrenal insufficiency is a possibility [16, 23].

Alesastine, loratadine, promethazine, diphenhydramine, chloropyramine, mebhydrolin, quifenadine should not be administered subcutaneously due to their strong irritating effect [29], and it is also necessary to avoid direct application of antagonists of H1 – histamine receptors to the skin due to the possible risk of sensitization [7, 1]. Zafirlukast should not be used simultaneously with acetylsalicylic acid, erythromycin and theophylline (physicochemical and pharmacokinetic incompatibility) [9]. Clarinase can cause drug dependence, and when administered with symptomatic agents or MAO inhibitors, there are possibility of hypertension and even hypertensive crisis [4, 1]. With the simultaneous use of ketotifen with oral hypoglycemic agents, thrombocytopenia is a possibility.

Thus, one of the common SE of drugs is drug allergy – a secondary heightened specific immune response to a drug and virtually all drugs can induce allergies. At the same time, ignorance of SE prevention measures of drugs is one of the reasons for the high frequency of allergic reactions to drugs. Despite some advances in the pharmacovigilance system (official observations of drug safety), adverse reactions of antiallergic drugs still remain one of the reasons for paradoxical situations in pharmacotherapy, especially with their unsustainable use. The information on the pharmacotherapy of allergies in this article has been analyzed and presented in order to drew the attention of pharmacologists, doctors and pharmacists to the potential risks of antiallergic drugs in order to comply with the rational conditions and characteristics of the use of widely used drugs for allergies The information on the pharmacotherapy of allergies in this article has been analyzed and presented in order to drew the attention of pharmacologists, doctors and pharmacists to the potential risks of antiallergic drugs in order to comply with the rational conditions and characteristics of the use of widely used drugs for allergies.

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