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PHARMACEUTICAL SCIENCES

MARKET RESEARCH R06A ANTIHISTAMINES FOR SYSTEMIC USE IN UKRAINE

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ABSTRACT

In the paper the analysis of the distribution R06A antihistamines for systemic use for ATC-classification has been conducted; the principal active substances, company-manufacturers and country-manufacturers of antihistamine drugs have been analyzed; a comparative analysis of the top list brands of antihistamines on sales volumes in monetary terms and in packages in 2015-2016 years has been conducted; the analysis of consumption volumes of antihistamines by using ATC / DDD – methodology has been conducted.

Keywords: antihistamines, active substances, systemic use, consumption volumes.

INTRODUCTION

The high prevalence of allergic diseases in recent decades is one of the major health problems worldwide. In Ukraine, according to official statistics allergic diseases have been reported in 10-15% of the population. Appointment of antihistamines today is the most common approach to allergy treatment. Antihistamine drugs inhibit the action of histamine, the main substance produced in the body during an allergic reaction (originator of the symptoms of this disease). Drugs in this group are used mainly in the treatment of allergic rhinitis and skin manifestations of allergy [1-3].

The reasons that cause allergies are numerous: pets, household dust, pollen, insect bites, food, and drug allergy, allergic to the sun, etc.

EXPERIMENTAL SECTION

Antihistamines first appeared in the 40s years of the twentieth century. Today, the Ukrainian pharmaceutical market they are well represented. Blockers H_1-receptors I generation have some properties that significantly limit their use. The most famous of them – is the effect on the central nervous system (CNS). Most often it manifests sedative effect. This is due to the ability of drugs to penetrate the blood-brain barrier and block the H_1-receptors in the CNS. Sedative effect inherent in varying degrees, all antihistamines I generation and can often lead to their cancellation [1-5]. Other undesirable effects of H_1-blockers on the CNS are dizziness, impaired coordination, and sense of lethargy, reduced capacity for learning and concentration, perception of new knowledge. Inhibitory effect on the central nervous system is enhanced while alcohol. Thus, the effect on the CNS significantly limits the use of antihistamines I generation, especially in patients whose work requires high concentration, quick decision-making and to students and pupils.

Low selectivity antihistamines of I generation, their impact on other types of receptors, primarily cholinergic, manifested by increased dryness of mucous membranes of the mouth, nose, blurred vision, urinary disorders, and incomplete binding to H_1 receptors short duration of clinical action, the possibility of tachyphylaxis in case of prolonged use creates certain difficulties in the application of drugs in this group. Thus, the development of tachyphylaxis indicates the need to replace them every 7-10 days. Adverse effects from the digestive tract may present with nausea, vomiting, diarrhea, decreased or increased appetite and so on. The body weight may increase in the case of the appointment for patients of traditional antihistamines. It should also consider the possibility of ventricular tachycardia in some patients during the use of these drugs. With care I generation antihistamines should be administered to patients with glaucoma, benign prostatic hyperplasia, in severe liver damage. The disadvantage of this group of drugs is the need to take them several times a day.

In the 70 years developed new highly selective antagonists of H_1 receptors. Due to the high selectivity towards H1-receptors and low penetration of the blood-brain barrier, they are deprived of most deficiencies characteristic of antihistamines I generation.

Recently obtained new data on the mechanism of action of modern antihistamines. It is proved that it is based not only on the well-known effect of blockade of H_1-receptors and is complex, including the impact on the different mechanisms of allergic inflammation. In high concentrations, the II generation antihistamines can block the release of inflammatory mediators basophilic granulocytes and mast cells; reduce the expression of adhesion molecules (ICAM-1) in epithelial cells influence the cytokines involved in the development of allergic inflammation [1-5].

Preparations II generation differ in pharmacokinetics, expressiveness the sedative effect, that determines features of their appointment for patients. In addition to high efficiency and safety of these drugs is

a significant advantage is convenience of application – most of them prescribed one time per day, duration of action is 24 hours.

The advantages of II generation antihistamines over traditional H_1-receptor blockers: high selectivity and affinity for the H_1 receptor; lack antagonistic action in relation to other types of receptors; low penetration across the blood-brain barrier; rapid onset of action; prolonged exposure (till 24 hours); lack development of tachyphylaxis; convenience of application.

However, there are some limitations in the appointment of the new generation of antihistamines. Mostly it concerns terfenadine and astemizole. A major disadvantage of the latter is the risk of complications of the cardiovascular system – serious ventricular arrhythmias in some patients, usually in the event of an overdose. Because metabolism of these drugs occurs in the liver, its necessary remember that if their purpose concurrently with drugs that are metabolized by the same enzyme systems (some macrolide antibiotics – erythromycin, clarithromycin, antifungals – ketoconazole, itraconazole, H_2-receptor blocker cimetidine, etc.) increased the concentration of the not metabolizained compound and risk of cardiotoxic effects. To avoid possible side effects of terfenadine and astemizole should strictly adhere to their dosing does not exceed the recommended daily dose is not administered simultaneously ketoconazole, itraconazole, erythromycin and other drugs. Do not use terfenadine and astemizole in patients with symptoms of hypokalemia, lengthening the interval Q-T on the ECG and the risk of ventricular arrhythmias, and in patients with hepatic impairment. Failure to comply with these rules may result in serious adverse effects on the cardiovascular system. In the case of taking II generation antihistamines like loratadine, cetirizine and akryvastyn, the risk of ventricular arrhythmias is minimal.

There are 172 medicines in 2015 in Ukraine in grope R06A antihistamines for systemic use. We have analyzed the range of antihistamines for systemic use for ATC-classification (fig. 1). Thus, 57% of medications (99 drugs) belong to the R06A X other antihistamines for systemic use; 26% medicines (45 drugs) belong to R06A E piperazine derivatives; 12% (20 drugs) belong to R06A A mono-alkyl ester; 4% (7 drugs) belong to R06A C Substituted ethylene diamines and 1% (1 drug) belong to R06A B Substituted alkylamines.

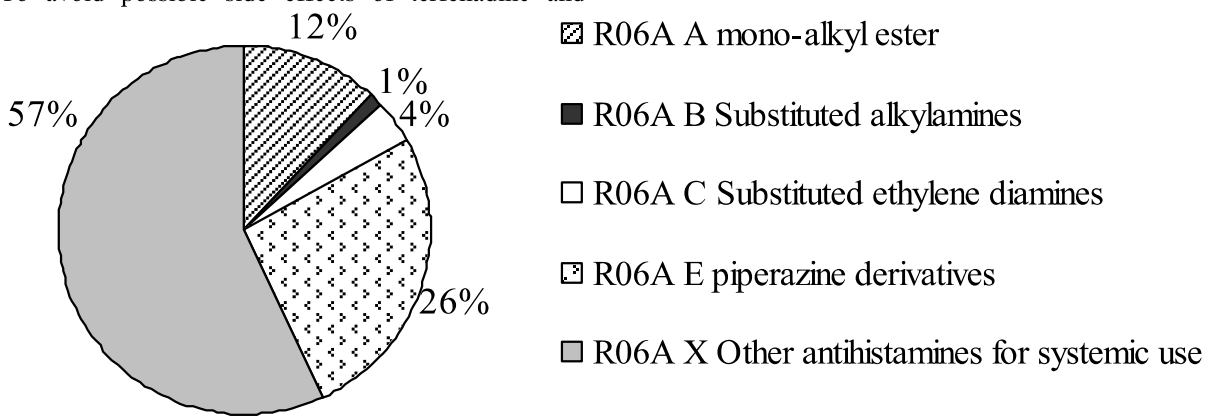

Fig. 1. Analysis of the distribution R06A antihistamines for systemic use for ATC-classification

It was also analyzed by us the distribution of antihistamines for their active substances on the pharmaceutical market of Ukraine (fig. 2).

It was set that most antihistamines on the Ukrainian pharmaceutical market have the active ingredients: R06A X13 Loratadine, R06A X27 Desloratadine, R06A E09 Levocetirizine, R06A E07 Cetirizine, accordingly 20%, 15%, 14% and 12% of all antihistamine drugs presented on the pharmaceutical market of Ukraine.

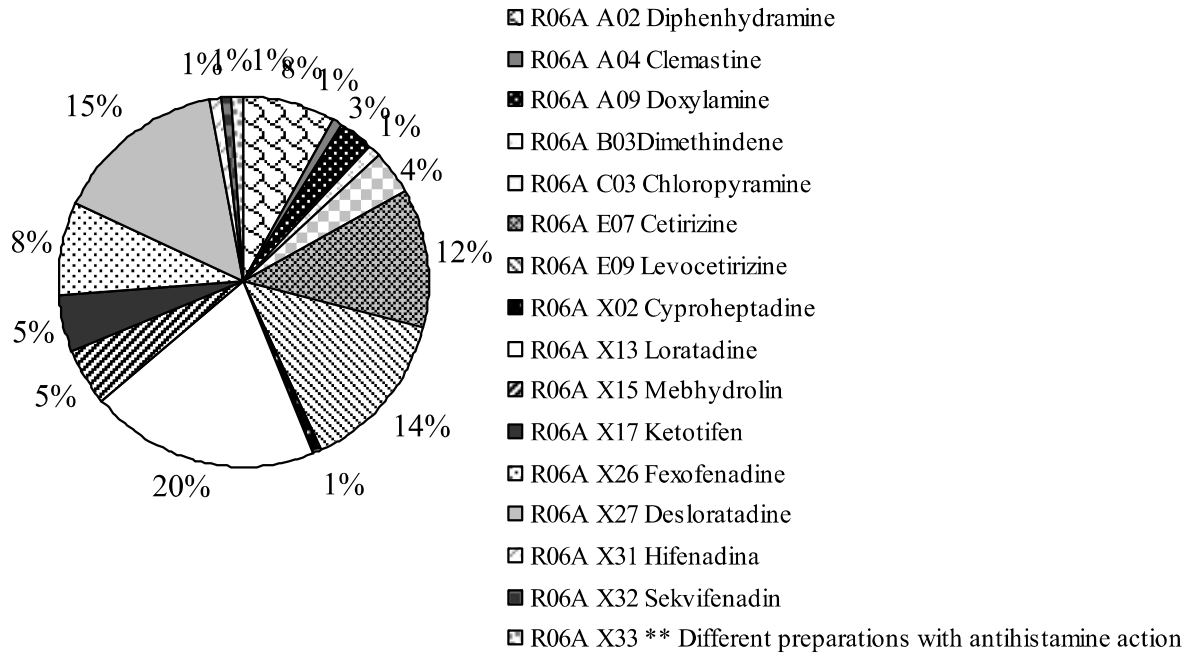

Fig. 2. Analysis of the distribution R06A antihistamines for systemic use for the active substance on the pharmaceutical market of Ukraine

Also we compared the consumption volumes of antihistamines by using ATC / DDD – methodology (table 1).

Table 1

Analysis of consumption volumes of antihistamines by using ATC / DDD – methodology

№	INN	DDDs/1000 persons/year		
		2014	2015	2016
1.	LORATADINE	830,30	901,60	913,04
2.	CETIRIZINE	444,21	567,10	594,73
3.	MEBHYDROLIN	655,53	627,42	573,46
4.	LEVOCETIRIZINE	197,50	336,36	415,15
5.	DEZLOPATADINE	98,85	171,86p	225,30

After analyzing the obtained data, it is established that the most consumption of antiallergic drugs are second generation with active ingredient Loratadine (consumption in 2016 – 913,04 DDDs/1000 persons /year). For such results there are a number of reasons: high efficiency and low cost; wide range of trade names; several types of dosage forms (this gives you the opportunity to expand the audience of consumers). It is revealed that in the domestic market, among antihistamines registered most drugs with active substance Loratadine – 20% (fig. 2).

Drugs with the active substance Cetirizine on consumption volumes occupy the second position (consumption 444,21 and 594,73 DDDs/1000 persons /year 2014 – 2016 respectively). It was set that 12% (fig. 2). The increasing demand for medicines with active ingredient Cetirizine is due to the fact that this drug has a number of advantages in its class: a pronounced anti-inflammatory and antipruritic effects; reduces the risk of development of asthma in people with allergic diseases; enables the use of long-term (18 months) courses without compromising efficiency.

During the 2014-2016 reduced consumption of Mebhydrolin. But DDDs indicators showed a high demand for these drugs. This is because the drug is presented on the market only Ukrainian manufacturers, it greatly reduces the cost. Mebhydrolin has 5 dosage forms, among them are children's doses. This facilitates safe use in pediatric practice. In addition, Mebhydrolin, attributed to antihistamines I generation, used in medical practice for quite a long time, which gives it certain advantages (for example the predictability of side effects).

Thus, ATC/DDD-analysis allowed us to estimate the consumption of these drugs for systemic use in established therapeutic doses, regardless of the cost of one package and the manufacturer. Based on this analysis we can observe that the market reduces the consumption of early generations. But consumption is increasing preparations of last generation (Deslorata-

dine, Levocetirizine), which have favorable pharmacokinetic characteristics and the optimal ratio of efficiency/safety. However, the volume of consumption for preparations of the second generation remains large (Loratadine, Cetirizine). They have a relatively low cost and relatively high pharmacological action, because basically presented on the pharmaceutical market of Ukraine in the form of generic medicines.

It was found by us that among registered 172 antihistamine drugs on the pharmaceutical market of Ukraine – 78 items (45%) are domestic medicines, and 94 drugs (55%) – imported medicines

There are such company-manufacturers and country-manufacturers of antihistamines on the Ukrainian pharmaceutical market: ABC Farmaceutici (Italy), Aesica Pharmaceuticals (Italy), Agio Pharmaceuticals (India), Aventis Pharma Deutschland (Germany), Aventis Pharmaceuticals (USA), Biofarm (Poland), Bioveeta Lab. (India), BMS (France), Cadila (India), Cadila Healthcare (India), Cipla (India), Dr. Reddy's (India), Egis (Hungary), Emcure Pharmaceuticals (India), FDC Ltd (India), Gedeon Richter (Hungary), Genom Biotech (India), GlaxoSmithKline (Egypt), Glenmark (India), Himanshu Overseas (India), Intas Pharmaceuticals (India), Kusum Healthcare (India), Lek (Slovenia), Micro Labs (India), Nobelpharma (Turkey), Novartis Consumer Health (Switzerland), Novartis Pharma (Switzerland), Novartis Pharma Production (Germany), Ranbaxy (India), Rottendorf Pharma (Germany), Rusan Pharma (India), Salutas Pharma (Germany), Sanofi-Aventis (United States), Sanofi-Synthelabo (UK), Schering-Plough Labo (Belgium), Sopharma (Bulgaria), Teva Czech Industries (Czech Republic), UCB Farchim (Switzerland), UCB Pharma (Italy), Unimax Laboratories (India), US Pharmacia (Poland), Zentiva (Czech Republic), Arterium (Ukraine), Astrafarm Ltd. (Ukraine), Biostimulator LLC (Ukraine), Biopharma Ltd. (Ukraine), Borschagovsky CPP PJSC (Ukraine), FZ Warsaw (Poland), Darnitsya PJSC (Ukraine), Zhytomyr PhF Ltd. (Ukraine), Zdorovya narodu Ltd. (Ukraine), Zdorovya LLC (Ukraine), Kiev Vitamin Plant PJSC (Ukraine), Red Star (Ukraine), Kusum Pharm LLC (Ukraine), Lekhim-Kharkov CJSC (Ukraine), HFZ Lugansk JSC (Ukraine), Monfarm JSC (Ukraine), OZ GNCLS Ltd. (Ukraine), JSC Olainfarm (Latvia), Stirolbiopharm Ltd. (Ukraine), Stoma JSC (Ukraine), JSC Farmak (Ukraine), Pharmstandard-Biolek (Ukraine), Phytopharm PJSC (Ukraine), Yuriya Pharm LLC (Ukraine).

During our research the comparative analysis of top list brands of R06A antihistamines for systemic use on sales volumes in monetary terms and in packages in 2015-2016 years was conducted (table 2).

RESULTS AND DISCUSSION:

After analyzing the results, it was found that the top three antihistamine medicines on sales volumes in monetary terms and in packages in 2015-2016 years were TSETRIN®, Dr. Reddy's (India), tablets film-coated 10 mg blister, №20; ERIUS®, Merck & Co (USA), tablets film-coated 5 mg blister, №10 and SUPRASTIN®, Egis (Hungary), tablets 25 mg, №20. Analysis table 1 shown that sales volumes in monetary terms and in packages for most drugs have been increased comparing to 2015 year.

Table 2

Comparative analysis top list brands of R06A antihistamines for systemic use on sales volumes in monetary terms and in packages in 2015-2016 years

№	Full name of the drug	2015		2016	
		Number of packages (pcs.)	Amount (thous. USD)	Number of packages (pcs.)	Amount (thous. USD)
1.	TSETRIN®, Dr. Reddy's (India), tablets film-coated 10 mg blister, №20	1 245 613,13	1 426,55	1 159 763,59	1 458,21
2.	ERIUS®, Merck & Co (USA), tablets film-coated 5 mg blister, №10	316 347,00	913,54	297 628,24	954,71
3.	SUPRASTIN®, Egis (Hungary), tablets 25 mg, №20	569 980,86	840,20	603 109,55	825,54
4.	FENISTIL, Novartis Consumer Health (Switzerland), drops of 1 mg/ml with a dropper bottle 20 ml, in a box, №1	336 684,73	648,78	413 058,26	843,63
5.	SUPRASTIN®, Egis (Hungary), the solution for injection 20 mg of 1 ml, №5	318 279,33	598,31	385 169,55	678,81
6.	EDEN, Farmak JSC (Ukraine), tablets film-coated 5 mg blister, №10	469 598,20	472,98	578 991,70	561,37
7.	ALERON, Actavis Group (Iceland), tablets film-coated 5 mg blister, №30	213 237,12	438,25	266 485,43	533,74
8.	KLARITIN®, Merck & Co (USA), tablets 10 mg, №10	216 643,65	513,80	223 829,60	500,33
9.	DONORMIL, Delta Medical emergency (Ukraine), tablets film-coated 15 mg tube, №30	193 364,26	398,78	239 061,04	484,70
10	L-TSET®, Kusum Healthcare (India), tablets film-coated 5 mg, №30	202 449,28	347,17	247 977,39	481,09

CONCLUSIONS:

1. The analysis of the distribution R06A antihistamines for systemic use for ATC-classification has been conducted.
2. The principal active substances, company-manufacturers and country-manufacturers of antihistamine drugs have been analyzed.
3. The analysis of consumption volumes of antihistamines by using ATC/DDD – methodology has been conducted.
4. The comparative analysis of the top list brands of antihistamine drugs on sales volumes in monetary terms and in packages in 2015-2016 years has been conducted.

References

1. Perederiy A.V., Yakovleva L.V. Formation of a national drug policy under implementation health insurance, 2015, 163.
2. Perederiy A.V., Iakovlieva L.V. Topical issues of new drugs development, 2015, 432.
3. Zaichenko G.V., Yakovleva L.V., Brukhanov T.O., Colossus O.N. Ukrainian Medical Journal, 2012, 6 (92), 120.
4. Biloshytska I.V., Tikhonov O.I. Journal of Pharmacy, 2013, 4, 48-51.
5. Biloshytska I.V., Tikhonov O.I., Kazarinova M.O. Journal of Pharmacy, 2010, 1, 16-18.

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ПОИСК СРЕДИ ПРОИЗВОДНЫХ АЛИФАТИЧЕСКИХ α-АМИНОКИСЛОТ СОЕДИНЕНИЙ, ОБЛАДАЮЩИХ ПРОТИВОМИКРОБНОЙ АКТИВНОСТЬЮ

THE SEARCH OF COMPOUNDS WITH THE ANTIMICROBIAL ACTIVITY AMONG DERIVATIVES OF ALIPHATIC α-AMINO ACIDS

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АННОТАЦИЯ

С целью установления зависимости антимикробного действия от природы заместителей в молекулах были протестированы N-гидроксиметильные, N,N-ди(гидроксиметильные) и N,N-ди(гидроксиметил)-N-метильные производные аланина, серина и треонина.

По отношению к грамотрицательным микроорганизмам и грибам исследуемые соединения проявили слабую или умеренную активность. Грамположительные бактерии более чувствительны к действию тестируемых производных аминокислот, при этом наибольшую антимикробную активность проявляют производные треонина.

ABSTRACT

With the aim of determining the dependence of the antimicrobial activity on the nature of the substituents in the molecules N-hydroxymethyl, N,N-di(hydroxymethyl) and N,N-di(hydroxymethyl)-N-methyl derivatives of alanine, serine and threonine have been tested.

The compounds studied have shown a weak or moderate activity in relation to gram-negative microorganisms and fungi. Gram-positive bacteria are more sensitive to the action of the derivatives of amino acids under research; moreover, derivatives of threonine exhibit the highest antimicrobial activity.

Ключевые слова: аминокислоты, противомикробная активность, антибиотикоустойчивость