ANTI-INFLAMMATORY AND ENDOTHELIUM PROTECTIVE EFFECT OF LONG-TERM PIOGLITAZONE INTAKE IN PATIENTS SUFFERING FROM BRONCHIAL ASTHMA CONCURRENT WITH ISCHEMIC HEART DISEASE

EFEKT PRZECIWZAPALNY I OCHRONNY WPŁYW NA ŚRÓDBŁONEK DŁUGOTERMINOWEGO STOSOWANIA PIOGLITAZONU U PACJENTÓW Z ASTMĄ OSKRZELOWĄ WSPÓŁWYSTĘPUJĄCĄ Z CHOROBĄ NIEDOKRWIENNĄ SERCA

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ABSTRACT

Introduction: Treatment of co-morbidities, including bronchial asthma (BA) and coronary heart disease (CHD), is a relevant issue of modern therapy.

The aim of the research is to study the impact of long-term intake of pioglitazone on the development of inflammation and ED in patients with BA concurrent with CHD.

Material and methods: The clinical study involved 50 people aged 40-75 who suffered from asthma concurrent with CHD. On the first day of the study, blood samples were collected and clinical examinations were performed, after which patients were randomized and divided into the control group who continued to receive only the standard therapy, and the study group, who received pioglitazone (Pioglar, Ranbaxy, India) 15 mg once a day along with comprehensive therapy. Re-examination was carried out in 6 months.

Results: It has been found that inclusion of pioglitazone in the course of standard therapy in patients with asthma concurrent with coronary heart within 6 months is a more efficient scheme than the course of standard therapies. According to the data obtained from the patients, there was a significant decrease in respiratory rate ($p<0.01$), levels of systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p<0.001$). Administering pioglitazone contributed to the improvement of respiratory function and airflow obstruction, increased FEV1 performance ($p<0.01$) and Tiffeneau index ($p<0.05$). In patients of the study group, intake of pioglitazone helped to reduce angina. Intake of pioglitazone showed a significant decrease in the frequency of angina pectoris FC II ($p<0.05$) and a significant increase in the frequency of angina FC I ($p<0.05$), increase in the rate of threshold load power ($p<0.05$). In assessing endothelium-dependent vasodilation of the brachial artery, it has been noted that intake of pioglitazone by patients with asthma concurrent with coronary heart disease resulted in a statistically significant increase in the diameter of the brachial artery by an average of 4% ($p<0.0001$), the maximum blood flow velocity (TAMX) by an average of 40 % ($p<0.0001$), Δ% diameter increase in the brachial artery ($p<0.0001$), and achieved positive indicators of RI ($p<0.0001$). In assessing endothelium-dependent vasodilation of brachial artery in patients treated with pioglitazone, there was a significant increase in the diameter of brachial artery on average by 5% ($p<0.0001$) after taking nitroglycerin, an increase in Δ% diameter of brachial artery ($p<0.0001$) and RI ($p<0.0001$). Inclusion of pioglitazone in the complex therapy for 6 months resulted in a significant decrease in the index of systemic inflammation hs-CRP ($p<0.0001$) and adhesion marker sVCAM-1 ($p<0.0001$), total cholesterol ($p<0.001$), triglycerides ($p<0.001$).

Conclusion: Thus, these data demonstrate the anti-inflammatory and endothelium protective effects of pioglitazone against the background of standard therapy in patients with BA concurrent with CHD within 6 months, which may enhance the clinical efficacy in the treatment of these diseases.

KEY WORDS: bronchial asthma, coronary heart disease, pioglitazone

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INTRODUCTION

Treatment of co-morbidities, including bronchial asthma (BA) and coronary heart disease (CHD), is a relevant issue of modern therapy. The high risk of cardiovascular events is directly related to the development of inflammation and endothelial dysfunction (ED), which are crucial in the damage of bronchopulmonary and cardiovascular systems [1].

In recent years, the idea of he correction of systemic inflammation and ED has acquired a leading role in the pathogenetic treatment of asthma concurrent with CHD [2], since the airway inflammation triggers the development of systemic inflammation and ED [3].

However, inhaled corticosteroids (ICS), which are used in the basic anti-inflammatory therapy, are not always clinically effective and pathogenetically feasible in BA against the background of CHD [4]. Earlier in the works of several authors [5, 6, 7] it has been demonstrated that thiazolidinediones have better clinical effects than inhaled corticosteroids in asthma.

It has been noted that thiazolidinediones reduce asthma exacerbation by 21% in patients with asthma and type 2 diabetes mellitus (DM), as compared with patients taking inhaled corticosteroids [6]. Therefore, special attention was drawn to medications of thiazolidinedione group, namely pioglitazone.

Pioglitazone is an agonist of nuclear peroxisome proliferator-activated receptor-gamma (PPARγ), providing pleiotropic effects, in particular antihyperglycemic, hypolipidemic, immunomodulating and anti-adhesion actions [7]. The data on the participation of thiazolidinediones in the regulation of inflammation and airway remodeling in asthma are being accumulated [8. 9. 10]. PERISCOPE study results have shown that pioglitazone prevents the progression of coronary atherosclerosis in patients with CHD against the background of type 2 diabetes [11]. However, there is still an open question as to the tactics of prescribing the medications of the group: duration, effectiveness and advantages of this therapy in patients with BA concurrent with CHD.

THE AIM

The aim of the research is to study the impact of long-term intake of pioglitazone on the development of inflammation and ED in patients with BA concurrent with CHD.

MATERIAL AND METHODS

The clinical study involved 50 people aged 40-75 who suffered from asthma concurrent with CHD. The study was conducted in the period from 2011 to 2013 on the basis of Poltava City Hospital No.1 and Research Institute for Genetic and Immunological Grounds of Pathology and Pharmacogenetics. The study protocol was approved by the Bioethics Committee of Ukrainian Medical Stomatological Academy. Before the start of the study, informed consent was obtained from all the participants.

Inclusion criteria were as follows: asthma of varying severity in remission, stable exertional angina.

Exclusion criteria were the history of chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), clinically significant cardiac rhythm and conduction disturbances, interventions, malignant arterial hypertension (AH), chronic heart failure (HF) of III-IV functional class (FC), acute cerebrovascular accident in the acute and subacute periods, diabetes mellitus (DM), glomerular filtration rate<60 ml / min, increased transaminase levels by 3 or more times, edema of any etiology, systemic connective tissue diseases, cancer and hematological diseases, severe infectious diseases, the presence of hypersensitivity to pioglitazone, inability to perform the spirometry protocol.

The diagnosis of asthma was confirmed on the basis of the criteria of Global Strategy for asthma management and prevention (GINA, revision as of 2009-2014) [12]. CHD was diagnosed in patients by the presence of angina of FC I-IV according to the classification of the Canadian Association of Cardiology and circulatory failure phenomena according to the classification of the New York Heart Association (NYHA).

At the screening stage, patients were examined to verify the diagnoses of asthma and coronary heart disease; to medical history and allergy data were collected, anthropometric measurements – weight, height, body mass index (BMI) (kg/m^2) were determined. Respiratory function (RF) was assessed by spirometry (spirograph "Kardioplyus", Ukraine) with bronchodilator test (salbutamol) by ATS and ERS criteria. Further, the electrocardiogram (ECG) data, and blood pressure (BP) – systolic (SBP) and diastolic (DBP) parameters were recorded. Bicycle ergometry was conducted on the bicycle ergometer Veloergotest 05 (Ukraine) by the method of stepwise load increase with the consequent extension in capacity under the supervision of electrocardiogram (ECG) and blood pressure. Power at the stage I was 150 kgm/min (25 W), at II – 300 kgm/min (50 W), at III – 450 kgm/min (75 W), at IV – 600 kgm/min (100 W), at V – 750 kgm/min (125 W), at VI – 900 kgm/min (150 W), the length of each stage was 3 min. Tolerance of CHD patients to exercise capacity was calculated according to the value of the threshold load capacity and volume of work performed. The threshold load capacity of 150 kg/min (25 W) was considered very low and consistent with angina of FC IV; 300 kgm/min (50 W) – low, FC III; 450 – 600 kgm/min (75-100 W) – medium, FC II; 750 kgm/min (125 W) and above – high exercise capacity, FC I. The criteria for termination of bicycle ergometry were conventional clinical or ECG signs of myocardial ischemia.

All patients to be included in the clinical trial were prescribed conventional treatment, and after the screening study – standard medical therapy, including inhaled corticosteroids (ICS) in the low, medium or high doses, depending on asthma severity in combination with inhaled long-acting β2-agonists (ILABA), amlodipine 5 mg once a day, atorvastatin 10 mg once a day, 75 acetylsalicylic acid mg once a day, isosorbide dinitrate 20 mg 2 times a day. Some patients received an additional number of the following medications as prescribed for more than 1 month before the inclusion: anti-leukotrienes – 2 persons (montelukast 10 mg once a day), 28 people depending on the blood pressure dynamics were taking angiotensin-converting enzyme inhibitors (ACE, enalapril 5 mg once a day). Patients were receiving the prescribed treatment during the month to achieve stable indicators for inclusion in the study. On the first day of the study, blood samples were collected and clinical examinations were performed, after which patients were randomized and divided into the control group who continued to receive only the standard therapy, and the study group, who received pioglitazone (Pioglar, Ranbaxy, India) 15 mg once a day along with comprehensive therapy. Re-examination was carried out in 6 months.

Assessment of endothelial function was performed using the method suggested by D.S. Celermajer et al. (1994) [13] on the ultrasound scanner Ultima PA expert (Rodman, Ukraine) in triplex mode with linear transducer of operating frequency of 05.12 MHz. Initially, the diameter of the brachial artery and the maximum linear blood flow velocity (TAMX) were measured.

The functional status of endothelium was evaluated using samples of postocclusive reactive hyperemia, where the

diameter of the brachial artery and the maximum linear blood flow velocity were determined initially and at the 60th second after 5 minutes of the brachial artery compression by the pressure of 50 mmHg above the systolic blood pressure (SBP) level in the patient. Further, endothelium-dependent vasodilation (EDVD) was calculated – the degree of increase in the brachial artery diameter (Δ% index) and reactivity index (RI) – the ratio of TAMX after the test to that of before the trial. To assess the myogenic mechanism for the regulation of vascular tone, the test with nitroglycerin was used, which was determined by the diameter of the brachial artery and TAMX after the test and 2 minutes after the intake of 0.5 mg sublingual nitroglycerin (NG). Afterwards, endothelium vasodilation was calculated as the degree of growth of the brachial artery diameter and RI (the ratio of TAMX before the test to that of after the test).

In the test of postocclusive reactive hyperemia, the dilatation of brachial artery, indicating the preservation of local mechanisms of vascular tone regulation, on the average is about 10% of the original diameter, while in the intake of NG – about 15%. The value of RI over 1.1 was regarded as a positive reaction of the blood flow, which indicates the preservation of endothelium function. The negative (the value of RI from 0.9 to 1.1) and paradoxical (the value of RI less than 0.9) types of reactions are considered abnormal and indicate ED. To eliminate the effect of nitrates on the results of diagnostic tests (tests with RH and NG), the medication was withdrawn one day prior to the event.

The level of systemic inflammation and active adhesion molecules was studied by determining the high-sensitivity C-reactive protein (hs-CRP), soluble forms of adhesion molecules of intravascular cell-1 (VCAM-1) and intercellular adhesion molecules-1 (ICAM-1) in accordance with manufacturer's protocols («DRG», «BioScience», USA).

Complete blood count, urinalysis, and biochemical analysis of blood (glucose, bilirubin, ALT, AST, total protein, urea, creatinine, residual nitrogen, triglycerides, total cholesterol, thymol) were conducted by conventional methods.

Statistical processing of the data was performed using the program «STATISTICA 6.0» (StatSoftInc., USA). Descriptive statistics of the research results is presented for qualitative characteristics in the form of frequencies, percentages, for quantitative – in the form of arithmetic mean values and standard errors. Significant differences between the indices were calculated for qualitative characteristics (frequencies) using Fisher's exact test and $\chi 2$, for quantitative – Student's t-test. For all types of analysis, the statistically significant differences at $p<0.05$ were considered.

RESULTS

The results showed that both groups of patients initially had significant differences in only a few parameters (Table I). Patients of the control group in contrast to the study group showed increased frequency in the indicators of HF of 1 degree (16 and 10 patients, respectively; $p<0.05$) and in the study group there were more patients with HF of 0 degrees (15 and 7 patients, respectively; $p<0.01$). Groups differed significantly from each other in terms of asthma duration ($p<0.02$), as well as by the frequency of respiratory distress of 2 degree (15 patients in the control group and 9 in the study group, $p<0.05$).

Table I. Clinical characteristics of examined patients with asthma against the background of coronary heart disease at the randomization stage

Parameter	Control group (n =25) Value, abs. (%)	Study group (n =25) Value, abs. (%)	Reliability
Gender: *Women Men*	7 (18) / 28 (72)	10 (40) / 15 (60)	>0.05 / >0.05
Age, *years*	56.64±1.69	54.52±1.73	>0.05
Height, *cm*	166.4±1.73	167.2±1.44	>0.05
Duration of the course:			
BA	16.4±2.15	9.72±1.6	**<0.02**
CHD	5.88±0.66	4.32±0.5	>0.05
BA concurrent with CHD	5.24±0.55	3.92±0.5	>0.05
Severity degree of BA:			
Intermittent	2 (8)	3 (12)	>0.05
persistent:			
mild	5 (20)	7 (28)	>0.05
medium severity	6 (24)	6 (24)	>0.5
severe	12 (48)	9 (36)	>0.05
Respiratory failure:			
0 degree	8 (32)	10 (40)	>0.05
1 degree	2 (8)	6 (24)	>0.05
2 degree	15 (60)	9 (36)	**<0.05**
Heart failure:			
0 degree	7 (28)	15 (60)	**<0.01**
1 degree	16 (64)	10 (40)	**<0.05**
2 degree	2 (8)	0	>0.05

Table II. Changes of clinical parameters in patients with bronchial asthma concurrent with coronary heart disease during the long-term treatment with pioglitazone

Parameter		Control group (n=25)			Study group (n=25)			Reliability
		Before treatment	After treatment	Reliability (p_1)	Before treatment	After treatment	Reliability (p_2)	
Weight, kg		83.20±3.68	82.8±3.68	>0.05	84.88±3.64	84.68±3.69	>0.5	$p_3 > 0.05$. $p_4 > 0.05$
Bronchodilator test, %		20.16±2.18	20.52±2.07	>0.05	17.26±2.03	16.44±1.65	>0.5	$p_3 > 0.05$. $p_4 > 0.05$
Bronchodilator test, ml		357.2±40.55	362.32±39.16	>0.05	347.4±37.71	342.84±31.31	>0.5	$p_3 > 0.05$. $p_4 > 0.05$
Systolic blood pressure, mm Hg		134.00±2.91	132.20±1.30	>0.05	132.00±1.47	125.60±1.31	**<0.001**	$p_3 > 0.05$. $p_4 <$ **0.001**
Diastolic blood pressure, mm Hg		85.40±1.74	83.8±0.86	>0.05	84.20±0.83	79.2±0.67	**<0.001**	$p_3 > 0.05$. $p_4 <$ **0.001**
Cardiac rate		71.52±2.16	69.80±1.89	>0.05	72.84±2.32	70.80±2.48	>0.05	$p_3 > 0.05$. $p_4 > 0.05$
Bicycle ergometry	Stress, W	100.00±4.9	109.00±4.21	> 0.05	107.00±4.8	120.00±2.45	**< 0.05**	$p_3 > 0.05$. $p_4 <$ **0.05**
	Angina: FC							
	I class	8 (32)	13(52)	>0.05	16 (64)	21 (84)	**<0.05**	$p_3 <$ **0.05**. $p_4 <$ **0.01**
	II class	13 (52)	10 (40)	>0.05	9 (36)	4 (16)	**<0.05**	$p_3 > 0.05$. $p_4 <$ **0.05**
	III class	4 (16)	2 (8)	>0.05	0	0	-	$p_3 <$ **0.05**. $p_4 > 0.05$

Note: here and in Tables 3, 4, 5: p1 - comparison before and after treatment in the control group, p2 - comparison before and after treatment in the study group, p3 - comparison before treatment in the control group to study group, p4 - comparison after treatment in the control group to study group.

Initially (Table II), the predominance of indicators of stable angina of FC I was revealed (16 and 8 patients, respectively; $p<0.05$) in the study group in contrast to the control group, whereas in the control group there were more patients with stable angina of FC III (4 and 0 patients, respectively; $p<0.05$).

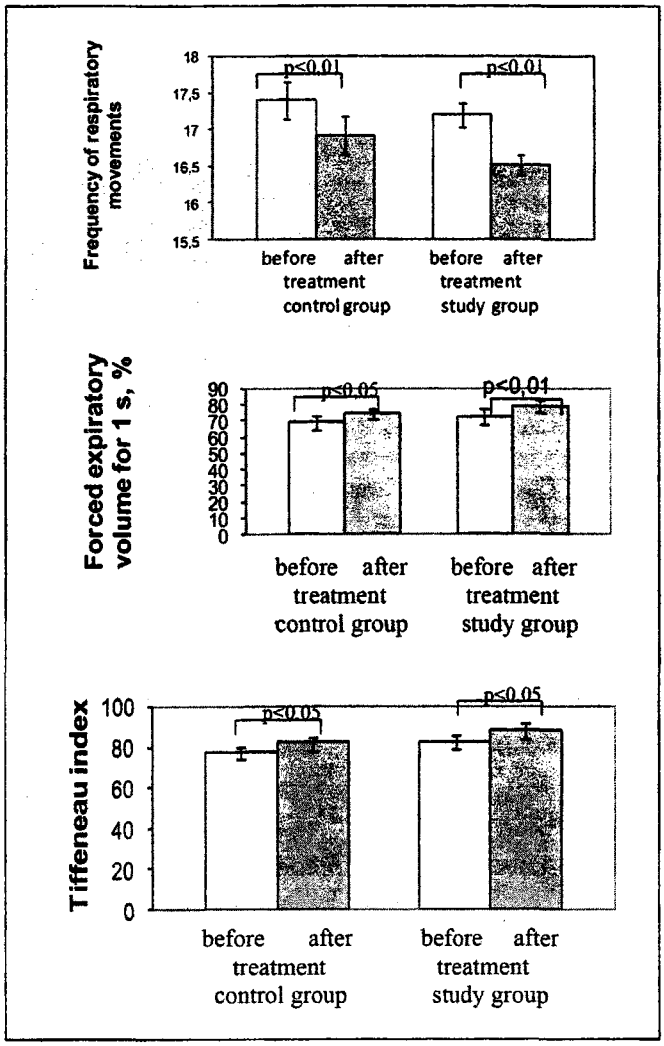
After randomization, the study group began receiving pioglitazone against the background of standard therapy for 6 months, and the control group continued to receive standard therapy.

It has been found that inclusion of pioglitazone in the course of standard therapy in patients with asthma concurrent with coronary heart within 6 months is a more efficient scheme than the course of standard therapies (Table II). Thus, according to the data obtained from the patients, there was a significant decrease in respiratory rate ($p<0.01$), levels of systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p<0.001$). Administering pioglitazone contributed to the improvement of respiratory function and airflow obstruction, increased FEV_1 performance ($p<0.01$) and Tiffeneau index ($p<0.05$) (Fig. 1). In patients of the study group, intake of pioglitazone helped to reduce angina. According to bicycle ergometry data, in patients with asthma concurrent with coronary heart disease, intake of pioglitazone showed a significant decrease in the frequency of angina pectoris FC II ($p<0.05$) and a significant increase in the frequency of angina FC I ($p<0.05$), increase in the rate of threshold load power ($p<0.05$).

Intake of the standard complex of medical therapy by patients with asthma concurrent with CHD also had a positive, but less pronounced effect. Significant decline in respiratory rate ($p<0.01$), increased rates of FEV_1 ($p<0.05$) and Tiffeneau index ($p<0.05$) (Fig. 1) have been registered in patients of the control group.

A statistically significant difference in the dynamics for the period of 6 months between the groups has been detected: patients with asthma concurrent with CHD in the study group had greater decrease in SBP ($p<0.001$) and DBP ($p<0.001$), reduction in the frequency of angina pectoris FC II ($p<0.05$) and increased frequency of angina pectoris FC I ($p<0.01$), increase in the rate of threshold load power ($p<0.05$) as compared with the control group.

The analysis of the data showed a significant improvement in the functional activity of endothelium and blood flow velocity in patients with asthma against the background of coronary heart disease receiving standard therapy with pioglitazone as compared to patients receiving only standard treatment (Table III). In assessing endothelium-dependent vasodilation of the brachial artery, it has been noted that intake of pioglitazone by patients with asthma concurrent with coronary heart disease resulted in a statistically significant increase in the diameter of the brachial artery by an average of 4% ($p<0.0001$), the maximum blood flow velocity (TAMX) by an average of 40 % ($p<0.0001$), Δ% diameter increase in the brachial artery ($p<0.0001$), and achieved positive indicators of RI ($p<0.0001$), while the intake of standard therapy resulted in a slight increase of TAMX on average by only 10% ($p<0.05$) and increase in the Δ% diameter of the brachial artery ($p<0.05$), increase of RI ($p<0.05$). In assessing endothelium-dependent vasodilation of brachial artery in patients treated with pioglitazone, there was a significant increase in the diameter of brachial artery on average by 5% ($p<0.0001$) after taking nitroglycerin, an increase in Δ% diameter of brachial artery ($p<0.0001$) and RI ($p<0.0001$), whereas in patients receiving standard therapy there was a slight increase in Δ% diameter of the brachial artery ($p<0.05$) and RI ($p<0.05$). It has been noted that in the dynamics of the 6 months therapy in the study group as compared with the control group there were



Note: p <0.05 in comparison of the group before and after treatment

Fig.1. Changes in the external respiration in patients with bronchial asthma concurrent with coronary heart disease during the long-term treatment with pioglitazone

significantly increased parameters of endothelium-dependent vasodilatation (diameter of the brachial artery after RH test ($p<0.05$), TAMX after RH test ($p<0.05$), RI ($p<0.05$) and Δ% diameter of the brachial artery ($p<0.05$)), endothelium-independent vasodilatation (diameter of the brachial artery after the test with NG ($p<0.05$), IR ($p<0.05$), Δ% diameter of the brachial artery ($p<0.05$)).

At the next stage of the research, the markers of acute inflammation and adhesion in the groups of patients were studied (Table IV). Inclusion of pioglitazone in the complex therapy for 6 months resulted in a significant decrease in the index of systemic inflammation hs-CRP ($p<0.0001$) and adhesion marker sVCAM-1 ($p<0.0001$). A similar significant decrease in the same indicators was identified in the control group after the standard therapy. A more pronounced decline by 1.94 times in the sVCAM-1 index was observed in the dynamics of 6 months in patients of the study group than in the control group ($p<0.0001$).

Tables V and VI show the changes in general clinical and biochemical blood parameters in groups of examined patients. According to the data presented in tables, inclusion of pioglitazone in the treatment complex for 6 months resulted in a significant reduction in the number of leukocytes ($p<0.01$), erythrocyte sedimentation rate ($p<0.05$), total cholesterol ($p<0.001$), triglycerides ($p<0.001$), reduced thymol test ($p<0.02$). In the control group after the standard therapy, there was stabilization of parameters, except for the significant increase in the concentration of glucose ($p<0.05$). In general, the groups did not significantly differ in terms of parameters after 6 months of treatment, except for significant reduction of ESR ($p<0.05$) and total cholesterol ($p<0.0001$) in the study group as compared with the control group.

CONCLUSIONS

Currently, the most effective medications in the treatment of asthma are inhaled corticosteroids, which reduce the frequency and severity of symptoms, exacerbations of the disease, improve exercise tolerance, and patient's quality of life. However, despite the apparent benefits, the therapy with inhaled corticosteroids has a number of drawbacks and limitations: intake of medications prevents correction of progressive decrease in the functional activity of the lungs and aggravation of atherosclerosis, as well as the need for life-long intake [4]. Therefore, especially important is the problem of finding a new alternative medication for the treatment of asthma against the background of coronary heart disease.

However, despite this fact [14], there are certain concerns about the use of medications in asthma due to the necessity of long-term intake and the use of high doses, since they can cause a number of undesirable side effects, such as suppression of cortisol synthesis, decreased bone density, oral candidiasis [4]. In addition, a small proportion of patients are resistant to anti-inflammatory effects of steroids. Consequently, there is a need for new anti-inflammatory medications to treat these diseases.

Our data showed that the inclusion of pioglitazone in the treatment complex of patients with asthma concurrent with coronary heart disease for 6 months was a more clinically effective scheme as compared with standard therapy. Favorable clinical effect of pioglitazone is due to improved respiratory function and airflow obstruction, decreased angina pectoris FC in patients with asthma against the background of coronary heart disease. It should be noted that in one of our earlier studies, the intake of pioglitazone for 3 months along with a standard course of therapy in patients with asthma against the background of coronary heart disease also led to the reduction of bronchial obstruction, systemic inflammation, and improved performance of EDVD and EIDVD [15]. To date, the effect of pioglitazone on the bronchopulmonary system is not completely studied. However, our findings are consistent with data from other experimental studies that show that taking pioglitazone in patients with BA reduces bronchial obstruction and inflammation in the lung tissues by suppressing the growth of smooth muscle

Table III. Changes in the functional activity of endothelium in patients with bronchial asthma concurrent with coronary heart disease during the long-term treatment with pioglitazone

Parameter		Control group (n=25)			Study group (n=25)			
		Before treatment	After treatment	Reliability (p_1)	Before treatment	After treatment	Reliability (p_2)	Reliability
Endothelium-dependent vasodilatation (test with RH)	Diameter of the brachial artery before the test, cm	4.23±0.07	4.19±0.04	>0.05	4.23±0.05	4.23±0.05	>0.05	$p_3 > 0.05$ $p_4 > 0.05$
	Diameter of the brachial artery after the test, cm	4.35±0.07	4.4±0.05	>0.05	4.37±0.06	4.58±0.06	**<0.0001**	$p_3 > 0.05$ **$p_4 < 0.05$**
	TAMX before the test, cm/s	6.32±0.4	6.7±0.35	>0.05	5.96±0.28	6.94±0.25	>0.05	$p_3 > 0.05$ $p_4 > 0.05$
	TAMX after the test, cm/s	6.01±0.38	6.65±0.36	**<0.05**	5.77±0.30	8.10±0.27	**<0.0001**	$p_3 > 0.05$ **$p_4 < 0.05$**
	RI	0.95±0.01	1.00±0.02	**<0.05**	0.96±0.01	1.17±0.02	**<0.0001**	$p_3 > 0.05$ **$p_4 < 0.05$**
	Δ% diameter of the brachial artery	3.08±0.21	5.01±0.32	**<0.05**	3.51±0.15	8.47±0.16	**<0.0001**	$p_3 < 0.05$ **$p_4 < 0.05$**
Endothelium-independent vasodilatation (test with NG)	Diameter of the brachial artery before the test, cm	4.25±0.07	4.21±0.04	>0.05	4.24±0.05	4.24±0.05	>0.05	$p_3 > 0.05$ $p_4 > 0.05$
	Diameter of the brachial artery after the test, cm	4.66±0.08	4.64±0.05	>0.05	4.65±0.06	4.87±0.07	**<0.0001**	$p_3 > 0.05$ **$p_4 < 0.05$**
	TAMX before the test, cm/s	5.95±0.39	6.67±0.34	**<0.01**	5.91±0.32	6.98±0.25	**<0.0001**	$p_3 > 0.05$ $p_4 > 0.05$
	TAMX after the test, cm/s	6.23±0.43	6.68±0.35	>0.05	6.24±0.36	5.95±0.25	>0.05	$p_3 > 0.05$ $p_4 > 0.05$
	RI	0.96±0.01	1.00±0.02	**<0.05**	0.95±0.01	1.18±0.02	**<0.0001**	$p_3 > 0.05$ **$p_4 < 0.05$**
	Δ% diameter of the brachial artery	9.86±0.21	10.34±0.31	**<0.05**	9.59±0.27	14.92±0.18	**<0.0001**	$p_3 > 0.05$ **$p_4 < 0.05$**

cells of the respiratory tract [5], reducing the synthesis and production of pro-inflammatory cytokines in the bronchoalveolar lavage [16]. The study by Narala V.R. et al. (2007) has found higher anti-inflammatory and remodeling bronchi effectiveness of pioglitazone as compared to dexamethasone [17].

Bronchial inflammation provokes the development of systemic inflammation, which, along with developing hypoxia, activates platelets, and developing oxidative stress – LDL oxidation with the formation of foam cells, which triggers changes in atherosclerotic endothelium. High levels of proinflammatory cytokines (IL-3, IL-4, IL-5, IL-6, IL-1 and TNF-α), neurotransmitters and proteins of the acute phase of inflammation (CRP) is a key marker in the formation of systemic inflammation and atherosclerosis [18].

Our study showed that the long term administration of pioglitazone for 6 months helped to reduce the inflammatory processes by inhibiting C-reactive protein, ESR, and sVCAM-1 adhesion molecule in the blood of patients with asthma concurrent with CHD. Our findings are consistent with other studies which have shown that activation of PPARγ receptors by pioglitazone in the cells of lung tissue causes reduction of allergic inflammation, the amount of eosinophils and mast cells, increased production of anti-inflammatory cytokine IL-10 (antagonist of proinflammatory cytokines Tx2 lymphocytes (IL-4 and IL-5) and IgE synthesis inhibitor), decrease in the synthesis of IL-4 and IL-5 in the smooth muscle cells and monocytes, the medication inhibits the expression of TNF-α, IL-6 and IL-1 [19]. The molecular mechanism by which pioglitazone regulates the inflammatory response is associated with the suppressed expression of the proinflammatory transcription gene, in particular members of the families of nuclear factor NF-kB, AP-1, STAT-1 and NFAT [20].

Endothelial dysfunction has an important role in the development of thrombosis, neoangiogenesis, vascular remodeling, intravascular activation of platelets and white blood cells. Predominant endothelial dysfunction depends on the development of immune-inflammatory processes. Activated endothelium with high level of expression of ICAM-1, VCAM-1 adhesion molecules is one of the earliest manifestations of atherosclerosis, which indicates the possibility of monocytes and T-lymphocytes to attack endothelium and penetrate the intima and induce exacerbation of inflammation and destruction processes [3].

In our study, it has been shown that the long-term use of pioglitazone for 6 months had a positive impact on improving the functional activity of endothelium

Table IV. The activity of inflammatory markers in patients with bronchial asthma concurrent with coronary heart disease during the long-term treatment with pioglitazone

Parameter	Control group (n=25)			Study group (n=25)			Reliability
	Before treatment	After treatment	Reliability (p_1)	Before treatment	After treatment	Reliability (p_2)	
hsCRP, *mg/l*	8.92±1.21	1.35±0.31	**< 0.0001**	10.07±1.25	0.98±0.31	< 0.0001	$p_3 > 0.05$, $p_4 > 0.05$
sICAM-1	418.59±25.37	423.64±39.60	> 0.05	319.14±23.01	384.77±27.92	> 0.05	$p_3 > 0.05$, $p_4 > 0.05$
sVCAM-1	3273.64±133.68	2132.17±69.77	**< 0.0001**	1488.18±74.50	1098.69±60.26	**< 0.0001**	$p_3 <$ **0.0001**, $p_4 <$ **0.0001**

Table V. Changes in blood count of patients with bronchial asthma concurrent with coronary heart disease during the long-term treatment with pioglitazone

Parameter	Control group (n=25)			Study group (n=25)			Reliability
	Before treatment	After treatment	Reliability (p_1)	Before treatment	After treatment	Reliability (p_2)	
Erythrocytes, $\times 10^{12}/l$	4.15±0.08	4.22±0.08	>0.05	4.22±0.06	4.23±0.05	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Hemoglobin, *g/l*	129.6±2.69	131.48±2.19	>0.05	133.32±2.21	131.16±2.77	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Color index	0.92±0.01	0.93±0.01	>0.05	0.94±0.01	0.94±0.01	>0.05	$p_3 <$ **0.05**, $p_4 > 0.05$
Leukocytes, *x* $10^9/l$	6.25±0.30	6.34±0.34	>0.05	6.53±0.35	5.55±0.26	**<0.01**	$p_3 > 0.05$, $p_4 > 0.05$
ESR, *mm/hr*	13.12±1.74	14.04±2.00	>0.05	12.12±1.50	8.56±1.15	**<0.05**	$p_3 > 0.05$, $p_4 <$ **0.05**
Eosinophils, %	2.08±0.33	2.44±0.46	>0.05	2.2±0.37	2.16±0.34	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Basophils, %	0.24±0.13	0.2±0.1	>0.05	0.24±0.1	0.24±0.09	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Stab, %	2.96±0.44	3.12±0.31	>0.05	3.36±0.42	2.6±0.17	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Segmentonuclear, %	57.76±1.9	61.16±1.76	>0.05	57.04±1.78	57.84±1.91	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Lymphocytes, %	29.28±1.58	27.56±1.63	>0.05	31.32±1.58	29.68±1.62	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Monocytes, %	7.04±0.5	6.28±0.29	>0.05	6.00±0.46	7.08±0.53	>0.05	$p_3 > 0.05$, $p_4 > 0.05$

and blood flow velocity, which can help to prevent the development of ED in patients with asthma concurrent with coronary heart disease. It has also been noted that the long-term use of pioglitazone contributed the antiadhesive impact by reducing the concentration of the sVCAM-1 molecule in the blood, and improved blood lipid profile by reducing total cholesterol and triglyceride levels in patients with asthma against the background of CHD, which in general can also significantly reduce the risk of atherosclerosis.

The analysis of modern experimental studies conclusively proves that the effect of pioglitazone on the functional state of cells involved in the atherosclerotic process in macrophages by inhibiting the production of inducible NO-synthase, matrix metalloproteinase-9, and in endothelial cells – IFN-γ-induced protein-10, monokine and endothelin-1, in the IFN-γ-induced T-cells – chemoattractant-α, and in T-lymphocytes – IL-2 [20, 21]. In a randomized clinical trial, the ability of pioglitazone to suppress the thickening of the intima-media in the carotid arteries has been pointed out [22]. In a multicenter study PROactive (Prospective Pioglitazone Clinical Trial In Macrovascular Events), which included 5238 patients with type 2 diabetes and macrovascular complications, the cardioprotective role of pioglitazone has been proven, which exceeded

Table VI. Changes of biochemical parameters of blood in patients with bronchial asthma concurrent with coronary heart disease during the long-term treatment with pioglitazone

Parameter	Control group (n=25)			Study group (n=25)			Reliability
	Before treatment	After treatment	Reliability (p_1)	Before treatment	After treatment	Reliability (p_2)	
Blood glucose, *mmol/l*	4.45±0.13	4.74±0.12	< **0.05**	4.7±0.16	4.42±0.11	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Cholesterol, *mmol/l*	5.37±0.17	5.15±0.08	> 0.05	5.37±0.16	4.69±0.07	<0.001	$p_3 > 0.05$, p_4 **<0.0001**
Triglycerides, *mmol/l*	1.26±0.09	1.19±0.08	> 0.05	1.37±0.12	0.99±0.08	< **0.001**	$p_3 > 0.05$, $p_4 > 0.05$
Bilirubin: Total, *mcM/l*	12.48±1.11	12.04±0.81	> 0.05	13.42±1.23	12.56±1.14	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Direct, *% of total*	3.64±0.41	3.32±0.23	> 0.05	3.9±0.4	3.64±0.39	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Indirect, *% of total*	8.84±0.73	8.72±0.61	> 0.05	9.52±0.85	8.8±0.79	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Total protein, *g/l*	72.72±1.23	73.64±0.92	>0.05	72.80±1.00	72.68±0.71	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Thymol test	1.72±0.08	1.84±0.12	>0.05	1.9±0.11	1.58±0.10	<**0.02**	$p_3 > 0.05$, $p_4 > 0.05$
Urea, *mmol/l*	5.46±0.25	5.47±0.35	>0.05	4.98±0.27	5.11±0.28	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Creatinine, *mcM/l*	80.48±2.79	83.12±3.24	>0.05	80.32±3.00	83.48±2.93	>0.05	$p_3 > 0.05$, $p_4 > 0.05$
Residual nitrogen, *mmol/l*	25.88±0.76	25.36±1.15	>0.05	24.40±0.82	24.41±0.78	>0.05	$p_3 > 0.05$, $p_4 > 0.05$

the efficiency of even the "gold standard" treatment, including antihypertensives (ACE inhibitors, beta blockers), oral antidiabetic (metformin, sulfonylureas, insulin), antiplatelet agents (aspirin, clopidogrel), and lipid-lowering agents (statins, fibrates). This study clearly demonstrated that pioglitazone can reduce the risk of death, myocardial infarction and stroke in patients with type 2 diabetes.

In our study, high tolerability of patients receiving pioglitazone was revealed; side effects and withdrawal of the drug were not detected, which demonstrates the effectiveness of this medication in the treatment of asthma and coronary heart disease.

Thus, these data demonstrate the anti-inflammatory and endothelium protective effects of pioglitazone against the background of standard therapy in patients with BA concurrent with CHD within 6 months, which may enhance the clinical efficacy in the treatment of these diseases. The use of pioglitazone in combination with the course of conventional therapy is a new, pathogenetically justified an effective treatment regimen of patients with asthma concurrent with CHD, which allows to significantly reduce the clinical manifestations, to inhibit the development of inflammation and endothelial dysfunction, establish adequate control over the course of the disease without causing negative manifestations of therapy and therefore can be recommended for use in clinical practice.

REFERENCES

1. Tattersall M.C., Guo M., Korcarz C.E. et al. Asthma predicts cardiovascular disease events: the multi-ethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol. 2015; 35 (6): 1520-1525.
2. Chih-Wei Y.; Te-Chun S.; Chiung-Ray L. et al. Asthma is associated with a subsequent risk of peripheral artery disease: a longitudinal population-based study. Medicine. 2016; 95(3): e2546-e2553.
3. Frostegerd J. Immunity, atherosclerosis and cardiovascular disease. BMC Medicine. 2013, 11: 117-130.
4. Chetta A., Olivieri D. Role of inhaled steroids in vascular airway remodelling in asthma and COPD. Int. J. Endocrinol. 2012; 2012: 1-6.
5. Patel H.J., Belvisi M.G., Bishop-Bailey D., Yacoub M.H., Mitchell J.A. Activation of peroxisome proliferator-activated receptors in human airway smooth muscle cells has a superior anti-inflammatory profile to corticosteroids: relevance for chronic obstructive pulmonary disease therapy. J. Immunol. 2003; 170(5): 2663-2669.
6. Rinne S.T., Feemster L.C., Collins B.F. et al. Thiazolidinediones and the risk of asthma exacerbation among patients with diabetes: a cohort study. Allergy Asthma Clin. Immunol. 2014; 10 (1): 10-34.
7. Anderson J.R., Mortimer K., Pang L. et al. Evaluation of the PPAR-γ agonist pioglitazone in mild asthma: a double-blind randomized controlled trial. PLoS ONE. 2016; 11 (8): 1-15.
8. Benayoun L., Letuve S., Druilhe A. et al. Regulation of peroxisome proliferator-activated receptor gamma expression in human asthmatic airways: Relationship with proliferation, apoptosis, and airway remodeling. Am. J. Respir. Critical Care Medicine. 2001; 164 (8 I): 1487-1494.
9. Kaidashev I.P., Kutsenko N.L. Retseptory, aktiviruyushchiye proliferatsiyu peroksisom, kak vozmozhnaya mishen' v lechenii allergicheskikh zabolevaniy. Klin immunol Allergol Infektol 2008; 3 (14): 59-63. Russian.

10. Kaidashev I.P., Bobrova N.A., Berkalo L.V., Kutsenko N.L. Novel approach for PPAR-γ stimulation in the treatment of bronchial asthma. 2009; 1-2 (13): 32-35. Russian.
11. Nissen S.E., Nicholls S.J., Wolski K. et al. PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA. 2008; 299 (13): 1561-73.
12. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (updated 2009, 2014).
13. Celermajer D.S., Sorensen K.E., Gooch V.M. et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992; 340: 1111-1115.
14. Leigh R., Mostafa M.M, King E.M. et al. An inhaled dose of budesonide induces genes involved in transcription and signaling in the human airways: enhancement of anti- and proinflammatory effector genes. Pharmacol. Res. Perspect. 2016; 4(4):e00243-e00261.
15. Byelan O.V., Borzykh O.A., Mamontova T.V., Kaidashev I.P. Clinical effectiveness of pioglitazone in the combination treatment of patients with asthma concurrent with coronary heart disease. Ter. Arkh. 2015; 87 (9): 44-51. Russian.
16. El-sakkar M.G., Barghash A. The efficacy of simvastatin and pioglitazone in a murine model of chronic asthma. Bull. Alex. Fac. Med. 2006; 42 (2): 51-59.
17. Narala V.R., Ranga R., Smith M.R. et al. Pioglitazone is as effective as dexametasone in cockroach allergen-induced murine model of asthma. Respir. Res. 2007; 8: 90-95.
18. Belan O.V., Kaĭdashev I.P., Borzykh O.A. The features of risk factors, systemic inflammation, and endothelial dysfunction in patients with asthma concurrent with coronary heart disease. Ter. Arkh. 2014; 86 (3): 34-9. Russian.
19. Kim S.R., Lee K.S., Park H.S. et al. Involvement of IL-10 in peroxisome proliferator-activated receptor γ-mediated anti-inflammatory response in asthma. Mol. Pharmacol. 2005; 68(6): 1568-1575.
20. Honda K., Marquillies P., Capron M. et al. Peroxisome proliferator-activated receptor γ is expressed in airways and inhibits features of airway remodeling in a mouse asthma model. J. Allergy Clin. Immunol. 2004; 113: 882-888.
21. Hanefeld M., Marx N., Pfutzner A. et al. Anti-inflammatory effects of pioglitazone and / or simvastatin in high cardiovascular risk patients with elevated high sensitivity c-reactive protein The PIOSTAT Study. J. Am. Coll. Cardiol. 2007; 49: 290-297.
22. Mazzone T., Meyer P.M., Feinstein S.B. et al. Effect of pioglitazone compared with glimepiride on carotid intimamedia thickness in type 2 diabetes: a randomized trial. JAMA. 2006; 296 (21): 2572-2581.

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