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THE CORRECTION OF CYTOKINE IMBALANCE AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH COPD WITH COMBINED GERD

Liakh O. I.¹, Turanica D. V.²

¹Uzhhorod National University, ²Uzhhorod city hospital, Uzhhorod

Abstract. *Introduction.* Gastroesophageal reflux disease (GERD) is a frequent concomitant pathology of COPD in which cytokine imbalance and endothelial dysfunction are observed.

The aim of the study. To study the effect of complex therapy including rebamipide on cytokine imbalance and endothelial dysfunction in patients with COPD with combined GERD.

Materials and methods. 60 patients treated in the pulmonology department of the Andrii Novak Transcarpathian Regional Clinical Hospital (TRCH) with a diagnosis of COPD II grade B in combination with GERD were under observation.

Results and their discussion. After the treatment, patients have a clinically significant decrease in systemic inflammation indicators, which is better seen in the group with the use of rebamipide.

Conclusions. The use of the drug rebamipide in the complex treatment of patients with COPD with combined GERD has a positive effect on the imbalance of cytokines and eliminates the dysfunction of the endothelium by the content of ET-1.

Key words: endothelium, prostaglandin E2, chronic obstructive pulmonary disease, rebamipide.

Корекція цитокинового дисбалансу та ендотеліальної дисфункції у хворих на ХОЗЛ із поєднаною ГЕРХ

Лях О.І., Туряниця Д.В.

Резюме. *Вступ.* Гастроєзофагеальна рефлюксна хвороба (ГЕРХ) є частою супутньою патологією ХОЗЛ, при якій спостерігається дисбаланс цитокинів і ендотеліальна дисфункція.

Мета дослідження. Вивчити вплив комплексної терапії, що включає ребаміпід, на цитокиновий дисбаланс та ендотеліальну дисфункцію у хворих на ХОЗЛ із поєднаною ГЕРХ.

Матеріали та методи. Під спостереженням перебувало 60 хворих, які перебували на лікуванні в пульмонологічному відділенні Закарпатської обласної клінічної лікарні (ЗОКЛ) імені Андрія Новака з діагнозом ХОЗЛ II ступеня В у поєднанні з ГЕРХ.

Результати досліджень. Після проведеного лікування у пацієнтів спостерігається клінічно значуще зниження показників системного запалення, що краще виявляється в групі застосування ребаміпиду.

Висновки. Застосування препарату ребаміпід у комплексному лікуванні хворих на ХОЗЛ із поєднаною ГЕРХ позитивно впливає на дисбаланс цитокинів та усуває дисфункцію ендотелію за вмістом ET-1.

Ключові слова: ендотелій, простагландин E2, хронічне обструктивне захворювання легень, ребаміпід.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease, manifested mainly by the following pulmonary syndromes: mucociliary insufficiency, bronchial obstruction, pulmonary emphysema, and general intoxication syndrome [14]. Patients with COPD, in addition to pulmonary manifestations, also have extra-pulmonary manifestations, the pathogenesis of which involves immunological inflammation, which leads to chronic hypoxia of tissues and leads to dysfunction of all organs and systems [9]. In the

edition of the Global Initiative for the Diagnosis and Treatment of COPD (GOLD, 2011), in its very definition, it is emphasized that comorbid conditions affect the overall severity of the disease [1].

The implementation of most links of the pathogenesis of various diseases is caused by a violation of the function of the endothelium [10]. The endothelium plays a key role in the stimulation of vascular tone, produces vasoactive substances and participates in the processes of homeostasis, hemostasis and inflammation. Endothelial



dysfunction (ED) is a violation of the regulation of vascular tone due to changes in the synthesis of biologically active substances, in particular, vasodilators (nitric oxide, NO) and vasoconstrictors (endothelin-1, ET-1). ET-1 is a biologically active peptide of a wide spectrum of action, which is one of the most important regulators of the functional state of the endothelium [13].

Risk factors for endothelium damage include inflammation with increased levels of pro-inflammatory cytokines (TNF- α , IL-8). Gastroesophageal reflux disease (GERD) is a frequent concomitant pathology of COPD [8] in which cytokine imbalance and endothelial dysfunction are observed [2, 5].

There is a large number of "trigger mechanisms" that cause immunological reactions that involve different types of blood cells and biologically active factors, so it can be assumed that in patients with COPD in combination with GERD, these mechanisms are also impaired, which determines the progression of this combined disease in terms of pathogenesis pathology [4]. Both in COPD and in concomitant gastropathies, the level of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-8 and interferon- γ increases by 15-20 times. In regenerative and restorative processes, there is an increased production of IL-4, prostaglandin F2 α [12]. Chronic obstructive pulmonary disease is characterized by a significant increase in the number of macrophages, neutrophils, CD8 + T-lymphocytes in the systemic bloodstream and in the area of inflammation, where leukotriene B4, IL-8, and TNF- α are the main mediators of the inflammatory process [4, 11].

The given data show that the combined pathology of the alimentary canal and the broncho-pulmonary apparatus is a complex pathological process. It requires a deeper study of the search for new alternative methods of treatment, since data on a successful combination of drugs that would simultaneously affect all links of the pathogenesis of COPD and GERD have not yet been found.

The aim of the study

To study the effect of complex therapy including rebamipide on cytokine imbalance and endothelial dysfunction in patients with COPD with combined GERD.

Materials and methods

60 patients treated in the pulmonology department of the Andrii Novak Transcarpathian

Regional Clinical Hospital (TRCH) with a diagnosis of COPD II grade B in combination with GERD were under observation. The average age of the subjects was 55 ± 1.64 years. Among the examined patients, men predominated by gender - 70.0% (42 out of 60). All subjects signed an informed consent, the methodology of which was in line with the Helsinki Declaration of 1975 and its revision in 1983 and was approved by Uzhhorod National University's Commission on Bioethics (Protocol №1 of 10.01.2020). The criteria for inclusion in the study were a confirmed diagnosis of chronic obstructive pulmonary disease (GOLD II) and/or GERD and age over 40 and under 70 years.

Exclusion criteria: age younger than 18 and older than 70 years, taking corticosteroids per os, presence of concomitant diseases of the respiratory, digestive, cardiovascular system, malignant neoplasms, refusal of the patient from the study.

The diagnosis of COPD was confirmed in accordance with the order of the Ministry of Health of Ukraine No. 555 dated 27.06.2013 "On the approval of clinical protocols for the provision of medical care in the specialty "Pulmonology" and the provisions formulated in the GOLD document [2011] [6]. The diagnosis of GERD was made in the presence of relevant complaints and the results of instrumental studies - a positive test with rabeprazole, fibrogastroduodenoscopy (FGDS) and intragastric pH-metry taking into account the Montreal Consensus (2006), the Gstadt guidelines on the strategy of treatment of GERD, as well as in accordance with domestic protocols for the provision of medical care (order of the Ministry of Health of Ukraine No. 943 dated 31.10.2013) [7].

General clinical, biochemical and serological tests were carried out in certified laboratories and commercial laboratories ("Dila" and "Sinevo"). FGDS was performed using endoscopy equipment with a video processor "Pentax" EPM-3300, during which any pathological changes in the esophagus and/or stomach and the degree of varicose veins of the esophagus were detected. The content of IL-4, IL-6, IFN γ , IFN γ /IL-4, TNF- α , endothelin-1, and prostaglandin E2 in blood serum was studied in all patients with COPD+GERD and in 30 healthy individuals of the control group by ELISA method - sets for quantitative measurement according to the methods proposed by the manufacturers: BIOSOURCE (USA) and DRG (Germany). The results were calculated using the Stat Fax device (USA). The results were calculated using the Stat Fax device (USA).

Within the framework of the conducted study, the effectiveness of complex therapy of patients with COPD in combination with GERD was evaluated. All patients received basic COPD treatment in accordance with existing domestic and international recommendations, which included long-acting beta-2 agonists, long-acting anticholinergics, as well as short-acting beta 2-agonists depending on the need.

Depending on the tasks and options for pharmacotherapy, patients are divided into two groups. The groups were representative in terms of age and sex. Group 1a (n=34) received complex therapy, which consisted of basic COPD therapy in combination with antireflux with the use of rebamipid, and group 1b (n=26) received basic COPD therapy in combination with antireflux without the use of rebamipide.

Antireflux therapy included: the appointment of a proton pump inhibitor (PPI) - rabeprazole in a dose of 20 mg in the morning, 30 minutes before meals, for 8 weeks with the transition to

on-demand therapy and itopride hydrochloride 50 mg 3 times a day for 1 month. Rebamipid was prescribed 100 mg 3 times a day for 1 month.

The effectiveness of the therapy was evaluated based on the dynamics of the clinical course of the disease and indicators of cytokines and endothelial dysfunction: IL-4, IL-6, IFN γ , IFN γ /IL-4, TNF- α , endothelin-1, prostaglandin E2.

The analysis and processing of the results of the examination of patients was carried out using the Statistics for Windows v.7.0 computer program (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the obtained results.

Results and their discussion

When studying the obtained laboratory data, it was established that in patients of groups 1a and 1b, before treatment, there was an increase in all acute-phase and pro-inflammatory indicators in comparison with the control group, where all these indicators were within the normal range at $p < 0.05$.

Table 1

Dynamics of cytokine indicators as a result of the treatment

Indication	To/After (1/2)	Group 1a (n=34)	Group 1b (n=26)	Control group (n=30)
Leukocytes $10^{12}/l$	1	12,1 $\pm$ 0,6	13,2 $\pm$ 1,1	6,5 $\pm$ 1,3
	2	7,3 $\pm$ 0,7	9,2 $\pm$ 0,8	6,3 $\pm$ 1,2
Neutrophils %	1	73,2 $\pm$ 2,4	74,1 $\pm$ 2,6	67,2 $\pm$ 3,1
	2	67,2 $\pm$ 1,7	68,1 $\pm$ 1,6	69,1 $\pm$ 2,8
ESR mm/year	1	16 $\pm$ 3,2	15 $\pm$ 3,7	6 $\pm$ 4,1
	2	11 $\pm$ 1,2	10 $\pm$ 2,5	5 $\pm$ 3,5
CRP mg/l	1	14,3 $\pm$ 2,8	16,2 $\pm$ 2,5	3,3 $\pm$ 1,5
	2	3,3 $\pm$ 0,6	3,4 $\pm$ 0,8	2,1 $\pm$ 1,9
IL-4, pg/ml	1	10,4 $\pm$ 2,1	13,5 $\pm$ 0,5	4,1 $\pm$ 0,6
	2	7,4 $\pm$ 1,1	8,5 $\pm$ 0,7	3,2 $\pm$ 0,4
Interferon gamma (IFN γ) pg/ml	1	118,2 $\pm$ 11,8*	120,1 $\pm$ 11,9*	12,1 $\pm$ 1,1
	2	21,1 $\pm$ 3,8	24,2 $\pm$ 5,5	13,2 $\pm$ 2,3
IFN γ / IL-4	1	23,7 $\pm$ 11,2*	29,3 $\pm$ 9,2*	7,1 $\pm$ 1,4
	2	6,6 $\pm$ 3,2	9,2 $\pm$ 2,2	6,7 $\pm$ 1,3
IL-6, pg/ml	1	17,4 $\pm$ 1,3*	18,5 $\pm$ 0,8*	6,8 $\pm$ 1,7
	2	7,1 $\pm$ 0,9	8,2 $\pm$ 1,3	5,3 $\pm$ 1,4

Notes: * - the difference is significant ($p < 0.05$); a – before treatment; b - after treatment.



Also, in the patients of the above-mentioned groups, an almost 10-fold increase in the level of IFN γ was noted in comparison with the control group, which suggests the activation of the cellular link of immunity in the case of eating pathology. An almost 3-fold increase in the ratio between IFN γ /IL-4 indicates the presence of an

imbalance in the immune system in patients with concomitant GERD. In groups 1a and 1b, a 2-fold increase in the pro-inflammatory cytokine IL-6 was found compared to the control group, which provokes an excessive and unregulated immune response, which in turn supports chronic inflammation even in the period of remission.

Table 2

Indicators of endothelium and prostaglandin E2 level before and after treatment

Indication	To/After (1/2)	Group 1a (n=34)	Group 1b (n=26)	Control group (n=30)
Endothelium -1 (ET-1), pg/ml	1	15,2 $\pm$ 1,1*	16,3 $\pm$ 0,3*	3,9 $\pm$ 0,2
	2	4,9 $\pm$ 0,3	5,5 $\pm$ 0,4	3,7 $\pm$ 0,4
Prostaglandin E2, pg/ml	1	490,4 $\pm$ 101,1*	510,5 $\pm$ 183,5*	1470,1 $\pm$ 102,4
	2	1300,3 $\pm$ 193,2	1188,1 $\pm$ 164,1	1500,3 $\pm$ 104,1

Notes: * the difference is significant ($p < 0.05$); a – before treatment; b – after treatment.

Regarding the levels of endothelin-1 in the serum of patients, its increase by 4 times was found in groups with comorbid GERD, in comparison with the comparison group, which is an indicator of endothelial dysfunction in patients with COPD combined with GERD, respectively at $p < 0.05$.

The content of prostaglandin E2 in the blood serum of patients in groups 1a and 1b was 3 times lower than in patients in group 2, which indicates a decrease in the protective properties of the mucous membrane of the gastrointestinal tract, respectively at $p < 0.05$.

After the treatment, patients have a clinically significant decrease in systemic inflammation indicators, which is better seen in the group with the use of rebamipide.

Thus, antireflux therapy in patients with COPD in combination with GERD eliminates the

main pathogenetic factor (acid reflux), which is an activator of the inflammatory process in the esophagus and respiratory tract.

Conclusions

1. The use of the drug rebamipide in the complex treatment of patients with COPD with combined GERD has a positive effect on the imbalance of cytokines and eliminates the dysfunction of the endothelium by the content of ET-1.

2. Complex antireflux therapy with the inclusion of the drug rebamipide contributes not only to the reduction of GERD symptoms, but also shows a tendency to normalize indicators of the function of external breathing, thereby improving the course of COPD.

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