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Inhibitors of Leukotrienes in Therapy of Severe Persistent Bronchial Asthma: For And Against

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Abstract: ***The important mediators of inflammation in bronchial asthma (BA) are leukotrienes (LT), which provide prolonged bronchoconstriction, secretion of viscous slime, neutrophil inflow, plasma exudation, and participate in immune reactions. LTS4, LTD4, LTE4 are called cysteine LT, differ from LTB4 by the presence of a peptide group. Anti-leukotriene drugs have been developed against cysteine LT, the most commonly used of which is montelukast sodium. The aim of the study was to study the concentration of LTB4 in serum and urine of severe asthma patients.When studying the level of LTB4 in patients with asthma severe persistent, it was revealed that during the exacerbation the concentration of LTB4 was 16.7 times (p <0.001) higher than normal. Against the background of the basal therapy, which included montelukast sodium, when exiting from the exacerbation, the level of LTB4 was reduced, but its index remained 12.3 times (p <0.001) higher than in healthy ones. At the same time, the values of LTB4 in patients who did not receive montelukast did not differ significantly from those in the patients to whom it was assigned, which confirms the insufficient effectiveness of montelukast for this type of radiation therapy, which determines the directions for finding ways to improve the effectiveness of treatment.***

Keywords: bronchial asthma, leukotrienes, antileukotriene preparations..

1. Introduction

The prevalence, difficulty of diagnosis, significant volume of therapy, development of complications cause the urgency of the problem of studying bronchial asthma.

One of the important pathogenetic mechanisms of bronchial asthma is chronic inflammation in the airways, which is mediated by immediate-type hypersensitivity reactions involving a significant number of cells and inflammatory mediators. Primary mediators, for example, histamine, already exist in mast cells, basophils and begin to secrete into the extracellular space immediately after the cell contacts the antigen. Secondary mediators are synthesized after contact of mast cells, basophils, lymphocytes and other inflammatory cells with antigen and are metabolites of arachidonic acid - eicosanoids [9, 11]. Slowly reacting substance of anaphylaxis, discovered in the 1960s. Was deciphered in the late 70's the last century were found leukotrienes (LT) C4, LT4, LT4 [15].

To date, 6 types of LT-A, B, C, D, E, F are known. In their chemical formula, there is a carboxyl group, the same number of carbon atoms in the main chain and the presence of four double bonds. At the same time, there are differences: leukotrienes C, D, E, F contain peptide (cysteine groups) in their structure, in contrast to leukotrienes A and B. Cysteine LT (Cys) are powerful pro-inflammatory mediators that lead to the development of bronchoconstriction. Leukotrienes are formed by the action of lipoxygenases from arachidonic acid. Lipoxigenes are found in the cytoplasm of different cells - in platelets, leukocytes, macrophages, obese cells. The most important of all enzymes is 5-lipoxygenase. Under the influence of the lipoxygenase complex, arachidonic acid is converted through a series of chemical reactions into leukotriene A4. The latter can be metabolized in two ways - to leukotriene B4 or cysteine LTC4, which, going into the extracellular space, is converted with gamma glutamate transpeptidase into LTD4, then LTE4 and then to LTF4.

LT plays an important role in the pathogenesis of asthma and / or allergic rhinitis, which may accompany or precede it. LTC4, LTD4, LTE4 - are powerful bronchoconstrictors, while affecting mainly the small airways, more than 6000 times the strength of histamine [11]. They can increase the tone of the smooth muscles of the gastrointestinal tract. LTB4 has a weak direct effect on smooth muscle, but by stimulating the cyclooxygenation of endogenous arachidonic acid and the formation of thromboxane in the airways, causes prolonged bronchospasm due to the development of edema, increased mucus secretion and influx of neutrophils. LTB4 causes significant reversible adhesion of leukocytes to the endothelium of postcapillary venules [15] promotes chemotaxis of neutrophils, causes plasma exudation, and participates in immune reactions.

Leukotrienes bind to receptors localized on the plasma membranes of cells [15]. Currently, 3 types of receptors have been isolated, with type 1 and 2 receptors binding LTC4, LTD4, LTE4, and receptor 3 - LTB4.

To prevent binding of leukotrienes to receptors, several ways can be used: to inhibit 5-lipoxygenase and initially to prevent the production of leukotrienes [6], and also to block cysteine LT receptors (removing their application point). An in-depth study of the pathogenesis of asthma, the identification of the role of radiation therapy in the implementation of inflammation and bronchospasm, stimulated the improvement of protocols for the treatment of the disease with the expansion of the

spectrum of basic drugs used for its treatment. Some of these are antileukotriene drugs [5].

Antileukotriene drugs are products that can block the enzyme 5-lipoxygenase-5-LO (that is, inhibit the synthesis of leukotrienes) a drug zileuton and selectively block leukotriene receptors. PT receptor antagonists block the action of cystenyl LT (LTC4, LTD4, LTE4) on target cells. The first antagonist of leukotriene receptors - FPL 55712 - was obtained in 1973. Further studies allowed the development of modern selective potent antagonists of the LTD4 receptors-for-firulukast and montelukast [1, 2, 5]. LT antagonists are considered as the most promising preventive agents in connection with pronounced anti-inflammatory and bronchodilator actions, as well as the ability to stop the progressive hypertrophy of the smooth muscles of the bronchi. They have an important place in the therapy of such clinical options for asthma, as well as bronchospasm attacks due to cold air.

The zileuton drug interrupts the production of LT, cysteine leukotriene antagonists - montelukast, pranlukast, zafirlukast block the application points of these LT.

The most effective anti-inflammatory protocol for treating all degrees of severity of persistent asthma is inhalation glucocorticosteroids (IGCS), they do not directly affect the level of leukotrienes, they do not completely suppress inflammation: even during the intake of IGCS in bronchial biopsy specimens there are signs nflammations with an increased content of activated eosinophils [10] have negative systemic effects, which often serves as a cause for steroidophobia and inhalation phobia, a failure to use them, especially in pediatric practice. The side effects of their use are oropharyngeal candidiasis, dysphonia, in rare cases, a decrease in the function of the adrenal cortex. Shortly after the cancellation or reduction of the dose of GCS in 80% of patients with asthma, increased bronchial hyperreactivity and relapse of the disease [6, 13, 14].

The use of antileukotriene drugs, which are also considered anti-inflammatory, is recommended by modern protocols for the treatment of asthma as an alternative therapeutic method for pulmonary persistent forms of asthma, especially in pediatrics. In addition, they must be added with insufficient control of asthma to IGCS, which increases the adherence of patients to basic therapy. One of the indications for the appointment of leukotrien modifiers is aspirin asthma and physical stress asthma, in which the leukotriene-new mechanism is identified as one of the leading ones [1]. At the same time, there are currently no studies or clinical data that would indicate a beneficial effect of drugs from the cysteine LT receptor antagonists group of patients with aspirin asthma compared to asthma with normal tolerability to aspirin [12]. However, for a specific genotype with polymorphism at the site that promotes cytotoxic leukotriene synthase C4 (characterized by a mutated allele C of LT synthase4), it is considered that the patient is predisposed to a more high response to the administration of montelukast. Treatment with a 5-LO inhibitor showed a moderate clinical improvement in aspirin asthma, especially with regard to alleviating nasal symptoms. Perhaps this is due to the genetic polymorphism of the gene that activates 5-LO.

The use of leukotriene modifiers helps reduce the frequency of β-2agonists and improves pulmonary function, reducing the frequency of sympathomimetic reception [6]. The appointment of modifiers of LT in patients with severe asthma allowed to reduce the dose of IGCS by 50% [10]. An important effect of the baseline use of antileukotriene drugs for patients with atopic asthma forms was the observed decrease in serum IgE concentration [1], which was not affected by the use of IGCS. The use of montelukast reduced the number of days spent in the hospital [16], the number of eosinophils in the peripheral blood [13], the decrease in the nasal peak expiratory flow rate (PEF) and nasal blockade according to the visual analogue scale [14]. However, all the results given were obtained in patients with mild or moderate asthma who underwent eosinophilic inflammation. Numerous studies have shown a decrease in the chemoattraction of eosinophils, inhibition of their migration through the vascular wall, a decrease in the survival of eosinophils and inhibition of the production of proinflammatory mediators, suppression of CysT-induced leukocyte adhesion, and expression of adhesive molecules [11]. All these effects are described for inhibitors of cysteine LT. The effectiveness of these drugs is determined by the blockade of cysteine LT receptors of two types – Cys LT1 and Cys LT2. The effectiveness of drugs according to the data of pharmaco-molecular studies is determined by the accuracy of the structure of the drug molecule structure of the receptor. The difference in the LTB4 structure in comparison with cysteine LT in the absence of a peptide fragment ensures inaccurate compliance of the montelukast antileukotriene drugs molecule with the receptor structure to LT B4, which may limit the effect of montelukast on the decrease in the concentration of this leukotriene [2].

Antileukotriene drugs is usually well tolerated by patients. In the 1990s, shortly after the introduction of cysteine LT receptor antagonists, reports emerged that they were triggering the development of the Charge-Strauss syndrome. However, this may be the result of a reduction in the dose of systemic glucocorticosteroids during the treatment with antileukotriene drugs against the background of the course of the Charge-Strauss syndrome, which had not previously been reliably diagnosed. Zileuton has a hepatotoxic effect. Before starting treatment with this drug, it is necessary to determine the concentration of hepatic enzymes in the blood serum and subsequently in the course of treatment to monitor their activity. There are reports of reactions between zileuton and several drugs (for example, terfenadine, warfarin and theophylline). The data show that co-administration of zileuton and warfarin significantly increases prothrombin time, which is associated with reduced warfarin clearance and an increased concentration of warfarin in the serum.

When using antileukotriene drugs, the effectiveness was not always shown, because Sensitivity can be individual: 1/3 of patients with asthma do not respond to antileukotriene drugs. Cases of the Charge-Strauss syndrome as a rare complication in steroid-dependent patients with asthma who were treated with antileukotriene drugs with a decrease in the dose of oral GCS were noted [7]. With prolonged use of antileukotriene drugs in some studies, there was a violation of the function of liver (pranlukast) [10].

In most studies of the efficacy of antileukotriene drugs, steroid-based patients were more often treated with mild or moderate forms of persistent asthma [6]. It should be noted that in these forms of asthma, patients most often have eosinophilic inflammation, while at the same time, severe infarction in the patient's airways has a neutrophilic inflammation [4, 8]. It is mediated by LTB4, the chemical formula of which differs from cysteine leukotrienes in the absence of a peptide group. Inaccurate compliance with the prescription and medicinal product reduces the effectiveness of the latter.

Perhaps the ineffective effect of combined treatment of IGCS with leukotriene modifiers in patients with moderate and severe asthma is covered in underestimation of the action of one of the important mediators - leukotriene B4, which is mainly a product of activated neutrophils, a stimulator of their chemotaxis [11]. Neutrophils in the airways and blood of bovine asthma have reduced abilities for phagocytosis, however, their significant role in the production of inflammatory mediators such as interleukin-8, which also stimulates the migration of neutrophils to the respiratory tract, increases the severity of inflammation [8].

The aim of investigation: to determine the dynamics of LTB4 in the serum and urine of patients with severe persistent bronchial asthma on the background of basic treatment with antileucotriene drugs.

Material and methods: 89 patients with moderate-onset exacerbation of asthma of severe persistent flow aged (34.5 ± 3.7) were eligible for the study, incl. men - 35 (39.3%), women - 54 (60.7%). All patients according to the type of therapy were divided into 2 groups - the main (45 people) and comparison (44 patients). The function of external respiration in patients was studied using a computer-assisted spirometer "Microlab" (MIR, Italy). The dynamics of the patients' condition was observed with the help of a peak meter ("Boehringer Ingelheim", Germany) with the determination of PEF and the calculation of its daily variability. Diagnosis of asthma was established in accordance with existing recommendations. All patients of the main group received baseline drugs during the exacerbation of asthma and at the outpatient stage according to the existing protocols, including antileukotriene drugs - montelukast sodium at a dose of 10 mg (1 tab.) per night. Patients of the antileukotriene drugs comparison group for different reasons (high cost, poor tolerance, etc.) were not assigned. In addition to the routine laboratory tests of blood, urine and sputum of patients, the concentration of LTB4 was studied in the blood serum and urine of patients upon admission, at discharge and after a month of follow-up by imunoenzyme analysis using standard commercial kits of LTB4 ELISA kit (Enzo Life Sciences, USA), and TxB2 - using the TXB2 ELISA kit (Enzo Life Sciences, USA). The measurements were performed on an Immunochem-2100 spectrophotometer (USA) at a wavelength of A = 405 nm.

To develop normative indicators, 29 healthy persons of the same age and sex were examined.

Results. When studying the function of external respiration, it was found that in patients with asthma, the volume of forced exhalation at the first second (FEV1) when entering the stationary division was (52.7 ± 3.8)%, in the morning hours PEF reached (234.2 ± 15, 8) l / min., in the evening - (316.3 ± 15.7) l / min, the daily variability of PEF - 35.1%. In sputum patients, with single eosinophils, it was found, on average, up to (47.3 ± 3.6) neutrophilic leukocytes in the field of vision. The definition of LTB4 revealed that when admitted to the hospital, its concentration in the blood serum in the morning hours was 16.7 times ($p < 0.001$) higher than the concentration of this eicosanoid in healthy individuals with lack of dynamics in the evening. In the urine of these patients, LTB4 was higher by 3.7 times than in healthy patients ($p < 0.01$), see the table 1.

Table 1.Dynamics of LTB4 concentration in serum and urine of patients in the main group in the morning and evening on the background of ongoing therapy

Index pg/ml	Index of healthy persons (n=29)	Patients of main group (n=45)		
		Before treatment	after treatment	1 month later after observation
		in the morning / evening	in the morning / evening	in the morning /evening
Serum	345,3± 37,6	5766,5±346,3* 5647,2±329,4*	4247,2±218,4* 3803,8±316,4*	3929,2±225,4* 2891,4±216,2*
urine	53,2± 4,7	197,1±4,3* 184,2±12,7*	238,8±14,2* 287,3±15,9*	367,7±22,1* 564,2± 34,1*

Note:

1. * - $p < 0.001$ when compared with the indices of healthy individuals;
2. __ $p < 0.01$ when comparing indicators before and after treatment

The FEV1 index had a strong positive correlation with the LTB4 concentration in the blood of patients in the morning hours ($r = +0.712$, $p < 0.05$), which indicated a negative effect of the indicated eicosanoid on the bronchial potency of patients. The PEF values also negatively correlated with the levels of LTB4 in the blood of patients ($r = +0.678$, $p < 0.05$) and ($r = + 0.664$, $p < 0.05$). Correlation of daily variability of PEF with concentration of LTB4 in the morning was negative of average force ($r = -0.227$, $p < 0.05$).

At discharge, the PEF level became equal to (362.6 ± 21.4) l / min, evening - (451.7 ± 19.5) l / min, variability PEF - 24.5%. Morning level of LTB4 decreased by 1.4 times from the initial, but remained higher than in healthy ones by 12.3 times ($p < 0.001$). Evening LTB4 index was 11.0 times ($p < 0.001$) higher than in healthy ones. Correlation connections of morning and evening PEF values retained their directionality, but somewhat decreased strength, respectively: ($r = +0.527$, $p < 0.05$) And ($r = +0.476$, $p < 0.05$). The daily variability of PEF negatively correlated with the morning values of LTB4 ($r = -0.426.9$, $p < 0.05$).

After 1 month of observation, the concentration of LTB4 in the blood serum of patients with astma of the main group decreased from the level at discharge of 2.1 times from the baseline values ($p < 0.05$), but remained above the norm 11.4 times ($p < 0.001$). PEF in the morning in the patients of the main group was 425.3 ± 23.9 l / min., in the evening - 502.7 ± 18.23 l / min., with the daily viability 18.2%. The correlation dependence of the daily variability of PEF and the morning concentration of LTB4 was of moderate strength, however, it changed the sign to positive, which is obviously related to pathogenetically significant changes in the LTB4 value for bronchial potency in patients. When studying the cellular composition of patients' expectorated sputum, it was found that up to 27.3 ± 3.6 neutrophils remained in the sputum in the patients of the main group. In the urine of patients in the main group, the concentration of LTB4 increased during the follow-up period, along with a decrease in blood serum.

When analyzing the dynamics of LTB4 in patients of the comparison group, it should be noted that during the periods of observation there were unidirectional changes with those in the patients of the main group. At the beginning of treatment, there was no difference in LTB4 in all patients. The level of LTB4 in the morning hours at discharge in the patients of the comparison group was 10.2% higher in the main group than in the main group, and in the evening group it did not differ from those in the main group. At patients of the basic group morning parameter LTB4 1 month later dispensary follow-up was also lower by 10.8% than in the comparison group, but also remained higher than normal in 12.6 times ($p < 0.001$), which is insignificantly different from the index in the main group. In the urine of the patients, the comparison groups were

Table 2 **Dynamics of the concentration of LTB4 in the blood serum and urine of patients in the comparison group in the morning and evening against baseline therapy**

Index pg/ml	Index of healthy persons (n=29)	The patients of comparison group (n=44)		
		Before treatment	after treatment	1 month later after discharge
		in the morning / evening	in the morning / evening	in the morning /evening
Serum	345,3±37,6	5749,3±314,5* 5698,8±297,4*	4692,3±227,6* 3905,1±309,2*	4352,7±262,4* 3078,6±242,3*
urine	53,2±4,7	203,4±4,9* 189,1±11,8*	289,2±13,9* 291,5±16,3*	413,7±22,4* 597,8± 36,1*

Note: 1. * - $p < 0.001$ when compared with the indices of healthy individuals;

2. __ $p < 0.05$ when comparing indicators before and after treatment

There are the same changes as in patients of the main group, with slightly higher LTB4 indices.

Our data are consistent with the results of a study of the activity of inhibitors of leukotrienes obtained by other authors, indicating that there is no significant effect of the inhibitor of cysteine LT montelukast on the level of LTB4 [1, 2, 11] and slightly different from the results obtained in the study of LTB4 in patients with asthma, combined with chronic nettle, where a positive effect of antileukotriene drugs on reducing the concentration of LTB4 was shown [3].

Thus, ALP are indicated for the treatment of asthma of mild and moderate severity, with combination of asthma and allergic rhinitis, allergic rhinitis and nasal polyps, asthma, asthma. In patients with severe persistent asthma during an exacerbation in sputum there is an increased amount of neutrophils, an increase in the meanings of LTB4 in the serum with its elevated urinary parameters. Elevated levels of LTB4 negatively affect on the bronchial potency of patients. In the period of exacerbation of asthma, there is a significant difference between the morning and evening concentrations of LTB4. The administration of antileucotriene montelukast preparation with a predominant effect on cysteine LT did not significantly affect the concentration of this leukotriene in the blood and urine of patients, its levels remained significantly elevated. This fact may be one of the reasons for the insufficient achievement of asthma control in patients with severe persistent asthma and neutrophilic inflammation in the tracheobronchial tree, frequent exacerbations of the disease and requires the search for new directions in the treatment of severe asthma.

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