EFFICACY OF ANTILEUKOTRIENE THERAPY IN EXERCISE-INDUCED BRONCHOSPASM IN SKIERS AND BIATHLONISTS

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Though the evidence base on application of antileukotrienesin asthmatic patients with exercise-induced bronchoconstriction is plentiful, their efficacy in preventing of exercise-induced bronchospasm (EIB) in winter sports athletes without asthma remains insufficiently studied.

The aim of the investigation was to assess the efficacy of montelukast to prevent exercise-induced bronchoconstriction in skiers and biathlonists.

Materials and Methods. 92 sportsmen were examined in the preparatory period, and 78 — in the competitive period of an annual training cycle (average age 17.5±2.3 years). A control group comprised 64 healthy volunteers of the similar age, not involved in professional sports. EIB screening was performed using afield-test with training at subfreezing temperature with a dynamic spirometry assessment (ERF, MasterScreenPneumo, Jaeger, Germany). Fractional exhaled NO (FeNO) level (CLD 88 with Denox 88, Switzeland) as well as NO_2^-/NO_3^- (R&D Systems, USA) and 3-nitrothyrosine (Hycultbiotech, Netherlands) in the exhaled breeze condensate (EBC) were measured before and after the exercise. Urinary excretion of cysteinyl leukotriene E_4 (LTE_4) (AssayDesign, USA) was also studied using ELISA with the correction according to the creatinine level. Sportsmen with EIB were treated with montelukast 10 mg once daily during 10 days with the following control examination in the described manner.

Results. A total prevalence of EIB among the sportsmen in both training periods amounted to 6.5%, and was comparable with the rate in the control group. At the end of the montelukast therapy all the sportsmen demonstrated no signs of EIB. Before treatment post-exercise increase of FeNO was noted. In contrast, after the montelukast course post-exercise decrease in FeNO level (ΔFeNO=–22.9%) was registered. Significant changes in EBC NO_2^-/NO_3^-, 3-nitrothyrosine, as well as in urine LTE_4 excretion were not found. However, a total concentration of NO_2^-/NO_3^- tended to decrease mainly owing to NO_2^- fraction. Sportsmen with EIB were characterized by the highest LTE_4/FeNO ratio.

Conclusion. EIB prevalence among the winter sports athletes does not exceed that of the control group. Montelukast may be used for EIB prevention in skiers and biathlonists, and its application is accompanied by a marked clinical dynamics without any changes in EBC level of NO metabolites and urinary excretion of LTE_4 at the end of a 10-day treatment period.

Key words: exercise-induced bronchoconstriction; winter sports athletes; montelukast.

Findings of numerous investigations demonstrate an important role of cysteinyl leukotrienes (cys-LT) in obstructive bronchial pathology, and in exercise-induced bronchospasm (EIB), in particular [1]. A diagnostic criterion of this syndrome is the reduction of the forced expiratory volume in 1 s (FEV1) by 10% and more of the initial level during physical exercise or during 30 min after it [2]. The main functions of cys-LT are vasodilatation and increase of vascular permeability, broncoconstriction, and formation of superoxide anion in leukocytes. Thus, the most promising direction of the EIB pharmacologic correction and prevention in sportsmen is application of antileukotriene therapy. Zafirlukast, used 8 h before the exercise, became one of the first cys-LT receptor antagonists with the improved EIB protection properties in asthmatic children and adults [3, 4]. Treatment with zafirlukast 20 and 80 mg by the asthmatic patients with EIB prevented the development of bronchoobstruction

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during 2 and 8 h respectively in the exercise testing, compared to the control group, receiving placebo, but previously treated by inhaled glucocorticosteroids. Pranlukast and zileuton were determined to have similar properties [3, 5, 6]. However, montelukast became the most popular drug among antileukotrienes, first approved in 1998 in the USA as a basic preparation for treating asthma in adults and children from the first year of life [3]. Montelukast clinical efficacy against persisting inflammation in asthma has also been studied on the EIB model. The clinical effect of a single montelukast dose (10 mg) was found to be preserved for 24 h, though its blood elimination half-life is about 5 h [3]. It was also shown, that this drug was also effective when used for the prophylaxis of exercise-induced asthma in children compared to the combination of budesonide and formoterol [3, 4]. Though the evidence base on application of antileukotrienes in exercise-induced asthma is plentiful, the question of this therapy efficacy and the rate of prophylactic effect development in EIB in sportsmen without asthma remains insufficiently studied.

Therefore, it is thought to be vital to study the efficacy of montelukast for skiers and biathlonists with a diagnosed EIB.

The aim of the investigation is to estimate the efficasy of montelukast treatment in skiers and biathlonists with a diagnosed exercise-induced broncospasm.

Materials and Methods. Skiers and biathlonists aged 17.5±2.3 years, training in the Khanty-Mansiysk Olympic Sports Schools were examined during competitive (n=78) and preparatory (n=92) periods. The number of boys and girls, included in the investigation, was comparable. The control group comprised 64 healthy volunteers of the same age, who did not do sports professionally.

The study complies with the Declaration of Helsinki (the Declaration was passed in Helsinki, Finland, June, 1964, and revised in October, 2000, Edinburg, Scotland) and was performed following approval by the Ethic Committee of Khanty-Mansiysk State Medical Academy. Written informed consent was obtained from the patients' parents.

Pulmonary function tests (MasterScreenPneumo, Jaeger, Germany) were performed initially, at 1, 5, 10-th minute after intensive 60 min long outdoor training at subzero temperatures. EIB was registered if post-exercise FEV1 was decreased by 10% or more [1, 2].

Initial and post-exercise fractional exhale nitric oxide, ppb (FeNO) was analysed using CLD 88 with Denox 88, (Switzeland). The procedure was performed according to the ATS/ERS recommendations [7]. At the prescreening stage sportsmen with current and recent (⩽4 weeks) respiratory tract infections were excluded from the study.

Exhaled breathe condensate (EBC) was collected before and after the exercise, the specimens were kept at –80°C. The quantitative measurement of total NO_2^-/NO_3^- (TNN) and 3-nitrothyrosine was made using R&D Systems (USA) and Hycultbiotech (Netherlands) lab kits, respectively.

Urine specimens for cys-LT assessment were collected in the morning before the exercise testing, and were kept at –80°C. The urinary LTE_4 excretion (AssayDesigns, USA) was performed by ELISA with the correction according to the urinary creatinine.

For all EIB-positive sportsmen (n=11) montelukast therapy 10 mg daily was administered for 10 days. At the end of the treatment the whole set of examination procedures was repeated. Thus, the investigation may be called an open, nonrandomized study, conducted in one group with the control by the initial parameters.

Statistical data processing was done using Statsoft Statistica 10.0. The results are reported as mean ± SE. To assess the difference between independent samples Mann–Whitney U-criterion was used, Wilcoxon criterion was used for dependent samples. The correlation between the signs was evaluated by calculation of Spearman rank correlation coefficient. Differences were regarded as statistically significant when $p<0.05$.

Results. All EIB-positive sportsmen (n=11) were treated with montelukast 10 mg daily for 10 days. One female skier did not receive the prescribed treatment due to disagreement. At the end of the treatment exercise-testing was repeated with the registration of the pulmonary function tests, FeNO and previously mentioned NO methabolites in EBC.

Changes in FEV1 were revealed in the sportsmen after the montelukast therapy (Fig. 1).

Control testing after 10-day therapy did not reveal EIB criteria after exercise in all sportsmen (Fig. 2).

The initial level of FeNO was comparable in EIB-positive sportsmen before and after the montelukast treatment, however post-exercise dynamics of the value has changed after the treatment (Fig. 3).

At the end of the treatment course the TNN, nitrates and nitrites in EBC were lower than the initial levels (mainly due to nitrite fractions), however, after the exercise test increase in TNN mostly due to nitrites fraction was observed (Fig. 4, 5). Significant differences between the EIB-positive and EIB-negative sportsmen were not registered probably due to a small sample volume of the sportsmen with EIB.

The EBC 3-nitrothyrosine in the examined group of sportsmen tended to increase after the treatment by montelukast (Fig. 6). Levels of LTE_4 urinary exretion before and after the treatment were comparable.

Thus, application of montelukast for non-asthmatic sportsmen with EIB resulted in clinical and functional resolution of bronchoobstruction with no changes of LTE_4 urinary excretion and tendency to the decrease of the TNN.

The initial mean LTE_4/FeNO ratio in skiers and biathlonists was 9.4±1.1; in the control group — 4.9±0.4 ($p=0.006$). Fig. 7 shows the distribution of the

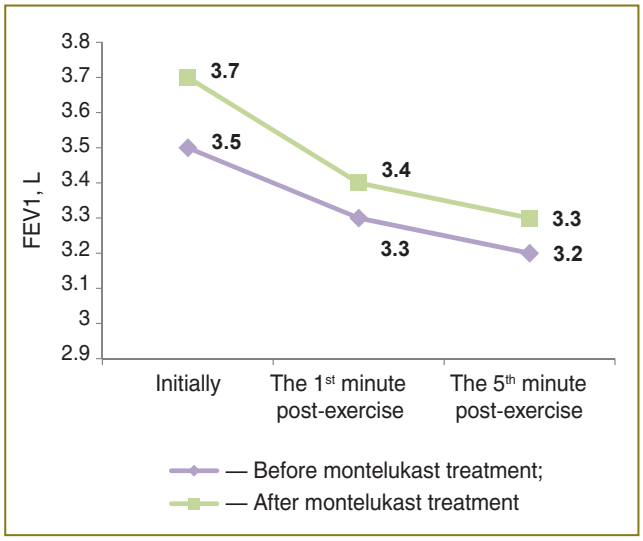

Fig. 1. Dynamics of FEV1 after 10-day montelukast treatment

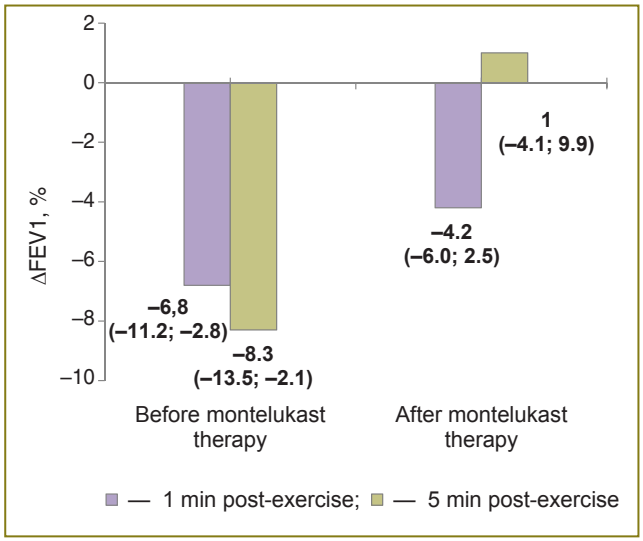

Fig. 2. Dynamics of ΔFEV1 after 10-day montelukast treatment
ΔFEV1

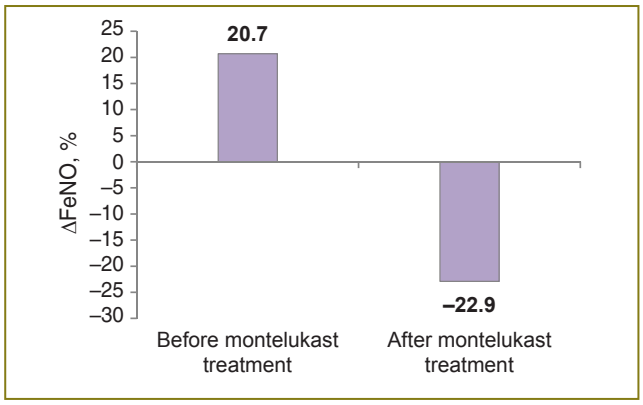

Fig. 3. Dynamics of ΔFeNO after 10-day montelukast treatment

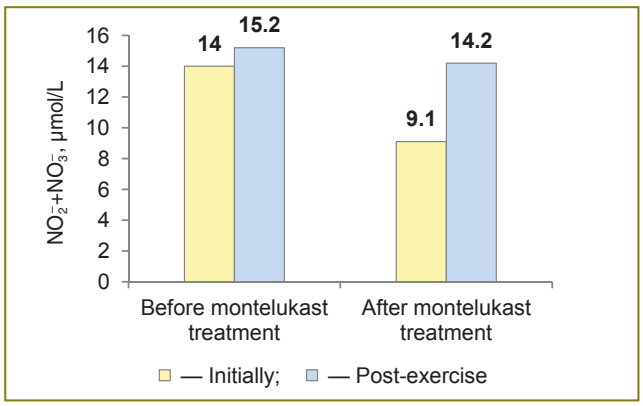

Fig. 4. Dynamics of EBC total nitrites and nitrates after montelukast therapy

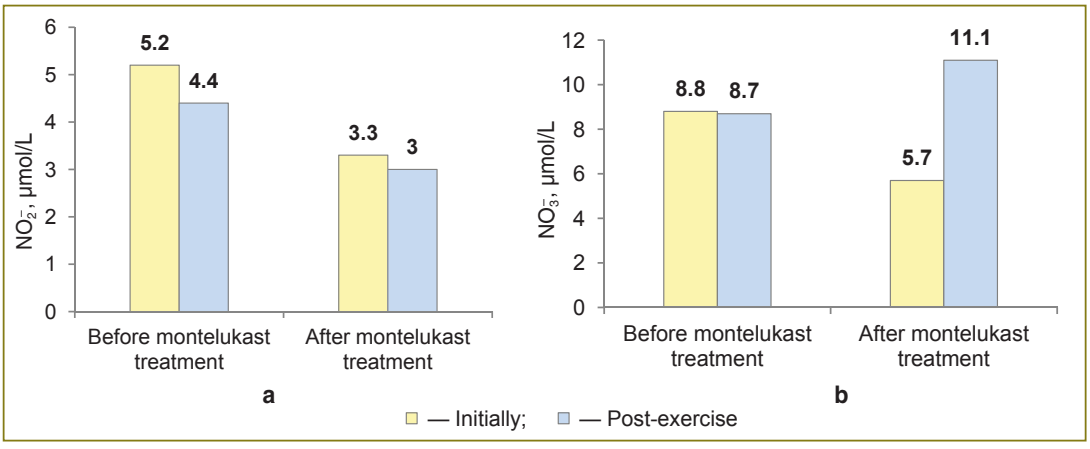

Fig. 5. Dynamics of EBC nitrites (*a*) and nitrates (*b*) after montelukast therapy

value depending on the presence/absence of EIB in the sportsmen and in the control group. Statistically significant gender differences were established for this ratio: 7.4±1.1 in males and 8.8±1.2 in females (p=0.02).

Discussion. Numerous clinical studies show the

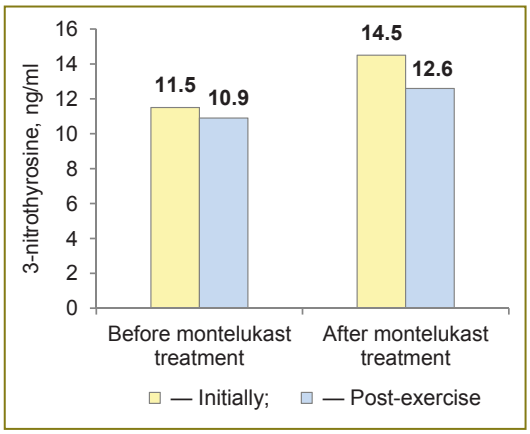

Fig. 6. Dynamics of 3-nitrothyrosine EBC level after montelucast therapy

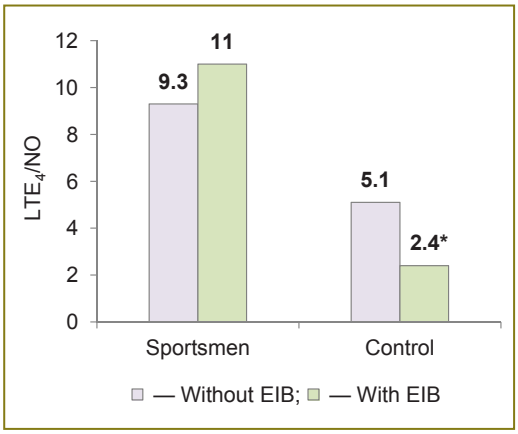

Fig. 7. LTE_4/FeNO ratio in EIB-positive and EIB-negative individuals; * — p=0.03 compared to EIB-negative controls

key role of cys-LT in the pathogenesis of EIB in asthma [1, 3]. Asthmatic patients with EIB demonstrated statistically significantly higher levels of cys-LT in EBC compared to EIB-negative asthma, the values increased after the exercise and correlated with EIB severity [8]. Cysteinyl leukotrienes are able to activate the leukocyte chemotaxis, adhesion of neutrophils to endothelium, release of proteases, and formation of superoxide anion by neutrophils, being expressed in the increase of capillary permeability. Moreover, cys-LT cause smooth musculature spasm, migration of eosinophils to the inflammation focus, hypersecretion of the mucus, proliferation of bronchial smooth muscles [1, 3].

The benefits of antileukotriene prevention of EIB by using montelukast include a good tolerance, a single-dose intake increasing the patients compliance, high efficacy and absence of resistance to the drug [1–3]. According to the placebo-controlled study by S. Steinshamn et al. [9], montelukast is capable to reduce the degree of broncoobstruction after exercise and to increase the performance status in the asthmatic runners with EIB. In the other placebo-controlled study [3] the efficacy of 12-week montelukast therapy was evaluated in 110 asthmatic patients with EIB using treadmill test to provoke bronchoconstriction. The test was conducted 20–24 h after the last dose on the 4-, 8-, 12th week of the treatment period and in 2 weeks after its ending. In the montelukast group significantly higher post-exercise FEV1 values were established. At the end of the therapeutic period in the placebo and montelukast groups ΔEFV1 were –30% and –18%, respectively. Patients treated with montelukast demonstrated more rapid recovery of the initial EFV1 values. The drug efficacy in all control points of the investigation was comparable, i.e. the development of the tolerance was not observed [3].

In the double blind placebo-controlled study of the montelukast efficacy in 11 physically active individuals with EIB [10] the drug was taken 6 h before the exercise test at the temperature –3°C and eucapnic hyperventilation test. Equally effective significant reduction of post-exercise FEV1 fall was noted in the montelukast group in both tests.

In the present study, EIB prevention by montelukast have been demonstrated in skiers and biathlonists, training at low temperatures. Thus, a mean value of ΔFEV1 after 10-day course of taking the preparation was not diagnostically significant (–4.2% at the 1st minute and 1% in 5th minute post-exercise). At the same time, the dynamics of the pulmonary function was not accompanied by any changes of LTE_4 level in the urine.

Speaking of the mechanisms of increasing cys-LT urine excretion in sportsmen, it is worth giving the results of the work by C. Caillaud et al. [11], aimed to study the serum and urine LTE_4 concentration dynamics i during intensive exercise in cyclists. The urinary excretion and serum level of LTE_4 have been shown to increase significantly in professional cyclists in response to exercise with an average level of VO_2 of 78% with the induction of mild hypoxemia (an average reduction of pO_2 was 15 mm Hg). This index remained unchanged in the group of untrained individuals with the similar exercise intensity and pO_2 reduction. There were no correlations between LTE_4 level and spirometry data, lung diffusion capacity and pO_2 in sportsmen. The investigators concluded that intensive exercise, accompanied by mild hypoxemia, may contribute to the increase of LTE_4 production, and the rise of this index is not connected with lung function changes. The data presented are correcpond with the findingsof present study, regarding the urine LTE_4 level in skiers and biathlonists compared to the group of individuals, who are not involved in professional sports.

The pre-exercise FeNO levels were similar in EIB-positive sportsmen before and after treatment with montelukast. However, important data, regarding ΔFeNO changes after the treatment, were obtained. Initially, post-exercise FeNO level in EIB-positive athletes was increased, but after 10-day treatment the decrease of post-exercise index was noticed. Overall,

changes in FeNO levels, concentrations of NO_2^-, NO_3^-, 3-nitrothyrosine in EBC before and after the treatment were not significantly different, owing to the low prevalence of EIB phenomenon among the examined sportsmen, and as a result, a small sample of treated skiers and biathlonists. However, the TNN together with ΔFeNO tended to reduce after the treatment. The obtained ΔFeNO dynamics suggests modulating properties of antileukotriene therapy for NO respiratory metabolism in EIB-positive winter sports athletes.

In recently publiched studies of EIB mechanisms, aimed at searching for the effective therapeutic approaches [12], the ratio LTE_4/FeNO was used as a predictor of efficacy of antileukotriene therapy. A higher ratio of LTE_4/FeNO was associated with the less marked decline in FEV1 in response to montelukast therapy, i.e. with the best preventive properties of the drug. The analysis of this ratio in the sportsmen and its correlation with the objective signs of EIB in present work does not allow to make a conclusion that the this ratio is a predictor of montelucast efficacy, as all treated sportsmen showed absence of diagnostically significant decrease in EFV1 after the exercise. However quite evident are higher levels of this ratio in winter sports athletes taken as a whole (regardless of EIB).

Conclusion. Group of leukotriene receptors antagonists of can be used as an alternative to the β2-agonists prophylaxis in skiers and biathlonists with EIB. Absence of significant contraindications and good tolerance are additional arguments in favor of antileukotriene application in non-asthmatic EIB-positive winter sports athletes.

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