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PATHOGENETIC APPROACH IN TREATMENT BRONCHIAL ASTHMA IN CHILDREN

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ABSTRACT

The article presents data on the clinical trials of local production of Montelukast (Republic of Uzbekistan). The purpose of the study is to assess the clinical efficacy and tolerability of montelukast preparations produced in Uzbekistan, in comparison with the drug Singlon, produced by Gedeon Richter JSC (Hungary). Methods. The clinical study was limited, comparative, open, controlled, randomized with four parallel groups. Studies were conducted in patients who are hospitalized in the pulmonology and allergology departments of the clinic of the Tashkent Medical Academy. The study involved 150 children aged 2 to 14 years with a diagnosis of intermittent, mild and moderate persistent bronchial asthma. Results: The clinical efficacy of the drugs was assessed in points for the improvement of clinical and laboratory data. The study showed a positive dynamics of clinical and laboratory parameters in all children who received Montelukast drugs. Conclusion. Studies have shown that local production montelukast is not inferior in its properties to foreign analogues and leads to a decrease in the level of cys-LT, IgE in children with asthma.

Key words: allergy, atopy, leukotriene receptors, bronchial asthma, children, montelukast.

INTRODUCTION

All over the world, including in Uzbekistan, bronchial asthma (BA) in children is an allergic disease that requires special attention. Epidemiological studies show that almost 1/3 of affected children experience 3 or more episodes of wheezing per year (which is considered the equivalent of an adult attack). Currently, there is a fairly wide range of effective drugs with a good safety profile and an affordable price for patients with this disease. Despite this, a large

proportion of patients receive inadequate treatment, which leads to a decrease in the quality of life, the formation of fixed bronchial obstruction, and even death [1,5]. Cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent anti-inflammatory eicosanoids released from various cells, including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT). CysLT type-1 (CysLT1) receptors are found in the airways (including airway smooth muscle cells and macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells) [2,11,12]. CysLTs are associated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include bronchospasm, mucosal secretion, vascular permeability, and recruitment of eosinophils. In allergic rhinitis, CysLTs are released from the nasal mucosa after exposure to the allergen during the early and late phase of the reaction, and are also associated with symptoms of allergic rhinitis. An intranasal test with CysLTs demonstrated an increase in nasal airway resistance and symptoms of nasal congestion[1,7,10].

Montelukast is an active substance that, when administered orally, binds with high affinity and selectivity to CysLT1 receptors. In clinical studies, montelukast inhibited bronchospasm induced by inhaled LTD4 at a dose of 5 mg. Bronchodilation occurred within 2 hours after oral administration. The bronchodilatory effect caused by β-agonists was complemented by the effect of montelukast. Treatment with montelukast inhibits both the early and late phases of bronchoconstriction due to antigenic stimulation. Montelukast, compared with placebo, reduces the level of eosinophils in the peripheral blood in adults and children. In a separate study, treatment with montelukast significantly reduced the number of eosinophils in the airways (determined by sputum analysis) and in peripheral blood, and improved clinical control of asthma [3,5,8,14].

In adult studies, montelukast 10 mg once daily, compared with placebo, showed a significant improvement in morning FEV1 (10.4% change from baseline compared to 2.7%), morning maximum expiratory flow rate (MOV) (24.5 L/min change from baseline vs. 3.3 L/min) and a significant decrease in total β-agonist use (change from baseline: -26.1% vs. -4.6%). Relief of daytime and nighttime asthma symptoms was reported by patients to be significantly better than placebo.

A clinical study was conducted to evaluate the use of montelukast for the symptomatic treatment of seasonal allergic rhinitis in patients aged 15 years and older with asthma and concomitant seasonal allergic rhinitis. In this study, montelukast (10 mg tablets, once daily) demonstrated a statistically significant improvement in daily rhinitis symptom scores compared to placebo. The 24-hour rhinitis symptom score is the average of the daytime (mean scores for nasal

congestion, rhinorrhea, sneezing, itchy nose) and nighttime (mean scores for nasal congestion on awakening, difficulty falling asleep, nocturnal awakenings) scores for rhinitis symptoms. Patients' and physicians' overall assessments of drug efficacy in allergic rhinitis were statistically better than placebo. Evaluation of efficacy in asthma was not the primary goal of this study [2,4,6,9,13].

In an 8-week study in children aged 6 to 14 years, montelukast 5 mg once daily compared to placebo significantly improved respiratory function (FEV1 8.71% vs. 4.16% change from baseline) indicator; change from baseline in morning MORV of 27.9 L/min vs. 8.2%.

A significant decrease in the measure of exercise-related bronchospasm (EIB) was observed at week 12 of the study in adults (maximum decrease in FEV1 22.33% for montelukast compared with 32.40% for placebo; time to recovery within 5% from baseline FEV1 44.22 minutes compared to 60.64 minutes). This effect was consistent throughout the 12-week study period. A reduction in ERF was also demonstrated in a short study in children aged 6 to 14 years (maximum reduction in FEV1 18.27% versus 26.11%; time to recovery within 5% of baseline FEV1 17.76 minutes versus from 27.98 minutes). The effect in both studies was demonstrated by the end of the drug dosing interval (1 time per day).

In aspirin-sensitive patients receiving concomitant inhaled and/or oral corticosteroids, montelukast treatment compared with placebo resulted in a significant improvement in asthma control (change from baseline in FEV1 8.55% versus -1.74% and change from baseline in reducing the total use of β-agonist -27.78% compared with 2.09%).

At the pharmaceutical market of the Republic of Uzbekistan today there are several names of montelukast preparations (Singlon, Gedeon Rixter, Hungary; Montular, Kusum, India; Miteka, India; Brizezi, India, etc.). The government of the republic pays great attention to the development of locally produced medicines. In the arsenal of pediatricians in Uzbekistan for the treatment of asthma, there are such drugs as Montexa (Nika Pharm, Uzbekistan), Neoclast (OOO Nobel, Uzbekistan), Astanol (Remedy Group, Uzbekistan).

PURPOSE OF THE STUDY

Evaluation of the clinical efficacy and tolerability of montelukast preparations manufactured in Uzbekistan, in comparison with the Singlon preparation, manufactured by Gedeon Richter JSC (Hungary).

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki, adopted in June 1964 (Helsinki, Finland), revised in October 2000 (Edinburgh, Scotland) and in accordance with the Law of the Republic of Uzbekistan "On

Medicines and Pharmaceutical Activities" , "The National Standard of Uzbekistan - GSR - Good Clinical Practice", taking into account the GSR rules used in international practice, the Regulations "On the procedure for conducting clinical trials and examination of materials for clinical trials of pharmacological and medicinal products" (Appendix 1 to the Order of the Ministry of Health of the Republic of Uzbekistan No. 40 dated 26 January 2021). Informed consent was obtained from the parents of the patients.

The clinical trial was limited, comparative, open, controlled, randomized with four parallel groups. The studies were carried out in patients undergoing inpatient treatment in the departments of pulmonology and allergology of the clinic of the Tashkent medical academy.

The study involved 150 children aged 2 to 14 years with a diagnosis of intermittent and mild persistent asthma. All children were divided into 4 groups: 1st group - children who received Astanol (Remedy Group, Uzbekistan) n=30; group 2 - children who received Neoclast (OOO Nobel) n=30; group 3, children who received Montexa (Nika Pharm, Uzbekistan) n=30; Group 4 (control) children who received the drug Singlon (Gedeon Rixter, Hungary) n=60. The average age of children was 6.8±2.1 years. The number of boys and girls included in the study was comparable. Children from 2 to 5 years of age were prescribed montelukast at a dose of 4 mg (chewable tablets), children from 6 to 14 years of age 5 mg (chewable tablets) once a day, at night, for 1 month.

All children underwent general clinical (collection of an allergic history, examination), physical examination, complete blood count, determination of total IgE, determination of the level of cys-LT in the urine, chest X-ray, peak flowmetry before and after the study.

Urine samples for the determination of cys-LT in the amount of 5 ml were collected in the morning. Quantitative determination of the final metabolite cys-LT (LTC4/D4/E4) in urine (reagent from Neogen, Ukraine) was performed by enzyme immunoassay. Measurement range: 0.04-8 ng/ml. Sensitivity: 0.04 ng/ml.

Statistical processing of the results was performed using the Statistica 10.0 software package. The data are presented as arithmetic mean values with an error of the mean. The difference in values was considered significant at $p<0.05$.

RESULTS AND DISCUSSION

The inclusion criteria for the trial were:

- patients of both sexes aged 2 to 14 years;

- diagnosis - intermittent, mild bronchial asthma;

- availability of informed written consent of the patient's parents (guardians) for the child's participation in a clinical trial

The criteria for exclusion from the trial were:
- the age of patients younger than 2 years and older than 14 years;
- the presence of contraindications to the appointment of Montelukast;
- severe bronchial asthma of a constant course (because monotherapy is not recommended)
- participation of the patient in other clinical studies within the last 30 days;
- lack of informed written consent of the patient to participate in the clinical trial.
The effectiveness of drugs was evaluated according to the following criteria:
- clinical improvement of the patient's condition (taking into account the dynamics of characteristic manifestations);
- reduction of manifestations and intensity of shortness of breath, cough, sputum.
- improvement of laboratory research data.
Evaluation of the effectiveness of the study drug was carried out on the basis of the above criteria in points according to the following scale:

Tolerability of drugs was assessed based on subjective symptoms and sensations, which the patient or his parents reported to the doctor, and taking into account objective data obtained by the doctor. The study took into account the dynamics of laboratory parameters. The tolerance of the study drugs was assessed in points on a scale from 0 to 4 points.

For the distribution of subjects into groups, the method of simple randomization was used. The initial table of distribution of patients by groups was formed on the basis of random numbers obtained using the MS Excel random number generation function.

After the patient was included in the study and assigned a serial number, the envelope corresponding to this number was opened, and the treatment contained in this envelope was administered.

Starting point of patient participation in the study: day of first administration of study drug or comparator

Treatment was described in detail in all patients included in the study.

Any therapy associated with comorbidities was recorded in the medical history and individual registration form.

All patient examination data were entered into the medical history, outpatient card and individual patient registration form.

Table 1

Dynamics of clinical manifestations of allergy in patients

Symptoms	Group 1 n =30		Group 2 n =30		Group 3 n =30		Group 4 n =60	
	before	after	before	after	before	after	before	after
Cough	2,76±0,02	0,73±0,03	2,23±0,04	0,4±0,01	2,83±0,03	0,5±0,01	2,9±0,04	0,1±0,01
Dyspnea	3.0±0,07	0,7±0,09	3,0±0,05	0,5±0,08	2.8±0,07	0,2±0,05	2,9±0,09	0,3±0,04
asthma attacks	2.1±0,07	0,1±0,005	2,1±0,08	0,08±0,003	2.1±0,05	0,06±0,002	2,7±0,09	0,04±0,001
p	*<0,001*		*<0,001*		*<0,001*		*<0,001*	

The severity of symptoms was noted in points:

0 - no sign *2 - moderately pronounced*

1 - weakly expressed *3 – expressed*

Table 2 shows that after the use of montelukast preparations, both domestically produced and in the comparison group, the number of eosinophils in peripheral blood decreased by 50% or more at the 4th week of therapy.

Table 2

Dynamics of the content of eosinophils in the blood (in %)

Preparations	**General blood analysis**	
	Eosinophils%	
	before	after
Group 1 (n =30)	5,6±0,20	3,1±0,12
Group 2 (n =30)	6,1±0,20	2,9±0,3
Group 3 (n =30)	5,9±0,20	2,3±0,2
Group 4 (n =60)	6,2±0,20	2,1±0,2

The study of the content of IgE in the blood of patients, as the main indicator of the allergological profile, also revealed a significant improvement in the results of the treatment with the tested drugs (p<0,001)

Table 3

Dynamics of the level of total immunoglobulin E in the blood (M±m)

Preparations	**IgE (ed/l)**	**IgE(ed/l)**
Group 1 (n =30)	381.6±4.5	236.4±4,07
Group 2 (n =30)	512.2±5.8	196.4±3,7
Group 3 (n =30)	481.2±5,5	245.3±4,11
Group 4 (n =60)	502.7±5,6	185,7±3,09

As can be seen from the data in Table 3, all children showed a decrease in the level of total IgE in the blood one month after taking the drugs. The greatest decrease was noted in children, groups 2 and 4 (p<0,001).

Numerous clinical studies indicate the key role of cys-LT in the pathogenesis of bronchial obstruction in bronchial asthma. Patients with bronchial asthma showed statistically significantly higher levels of cys-LT in the urine compared with healthy children.

During the study, we studied the state of the level of cys-LT in the urine in 52 patients.

Table 4

Dynamics of the level of cys-LT in urine (nm/l)

Preparations	$C_4D_4E_4$	$C_4D_4E_4$
Group 3 (n =30)	4.15±0.18	2.89±0.09
Group 4 (n =22)	4.23±0.2	1.92±0.06

Studies have shown that taking montelukast leads to a decrease in the level of cys-LT in the urine. At the same time, in children of the 4th group, a more significant decrease in the level of cys-LT was noted than in children of the 3rd group (p<0.05).

In children older than 5 years of age, a study of the peak expiratory flow rate was performed by performing peakflowmetry. The study of the PSV1 index (in %) did not reveal any significant changes during the entire study in all Groups. However, it should be noted that all children had positive changes in the value of this indicator. (Table 5).

Table 5

Dynamics of changes in PSV1 (in %) in children 5 years and older

Preparations	PFM1 baseline	PFM1 after treatment
Group 1 n =12	65,2±1,12	73,7±1,01
Group 2 n =17	64,3±1,01	75,1±1,03
Group 3 n =14	60,2±1,06	79,1±1,11
Group 4 n =22	58,2±1,12	77,7±1,09

Summing up the results of the studies, and after analyzing them, the values of the indicators of the effectiveness and tolerability of the drugs were derived, which indicate the equivalence of their action on the examined patients.

Table 6

Evaluation of the effectiveness and tolerability of drugs in points

Drug/Indicator	Efficiency	Portability
Group 1	2,9±0,01	3,9±0,06
Group 2	2,8±0,05	4,0±0
Group 3	2,8±0,1	4,0±0
Group 4	3,0±0,00	4,0±0

Conclusions. In accordance with the results of clinical trials and recommendations of international documents (GINA, 2015, 2018) [7,8], montelukast is recommended for use in mild BA as an alternative to ICS and in moderate BA in combination with ICS. The use of montelukast in pediatric practice will ensure the stability of the condition of children with bronchial asthma.

The data obtained allow us to conclude that Preparations montelukast produced in Uzbekistan (Montexa, Astanol, Neoclast) are effective drugs for the treatment of mild bronchial asthma in children from 2 to 5 years of age.

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