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Use of Antileukotriene Drugs in Treatment of Children with Bronchial Asthma

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Abstract.

There were examined 65 children with partially controlled and uncontrolled bronchial asthma (BA) in the exacerbation phase at the age of 5-7 years. Acute respiratory viral infections were often complicated by wheezing (49.2%) and pneumonia (16.8%). Unfortunately, most of these episodes were treated using antibacterial therapy despite normal values of the complete blood count and no infiltrative changes in the chest radiography. Children of Group I underwent basic therapy of BA in the form of inhaled corticosteroids (ICS), patients of Group II received antileukotriene drug – montelukast (Milukante) in addition to basic therapy of BA. When assessing the values of peakflowmetry a peak flow rate was found to be improved in all children ($p<0.001$), however, in children who additionally received montelukast better parameters of the average daily bronchial patency (ADBP) were observed 77.29±1.17% vs. 72.87±0.73% in Group I ($p<0.05$). There was a similar tendency when assessing the increase in the ADBP 19.9±1.1% and 23.35±1.18% in Group I and II, respectively. After inpatient treatment, patients were prescribed monotherapy with ICS (Group I) or montelukast (Group II) for 3 months. In children who received montelukast parameters of the ADBP were found to be higher 81.29±1.17% vs. 89.27±1.11% in Group I ($p<0.05$) and, accordingly, the assessment of general well-being was higher, too. Such differences between groups are explained by the fact that patients preferred taking montelukast to taking ICS.

Problem statement and analysis of the recent research

In recent years antileukotriene drugs have been widely used in treatment of many allergic diseases in general, and bronchial asthma (BA) in particular [1, 2, 4, 9,12].

Leukotrienes (LT) are biologically active mediators that are formed due to arachidonic acid metabolism via the 5-lipoxygenase pathway. They may be formed in eosinophils, basophils, mast cells, alveolar macrophages. There are two types of LT: cysteinyl LT (LTC_4, LTD_4, LTE_4) and hydroxyleukotrienes (LTB_4). Cysteinyl LT play an important role in the pathogenesis of BA causing bronchoconstriction, stimulating bronchial mucus secretion, reducing mucociliary clearance, increasing vascular permeability and inducing the migration of eosinophils and neutrophils to inflammatory focus [7].

Antileukotriene drugs are divided into four groups: 5-lipoxygenase inhibitors; FLAP inhibitors binding to arachidonic acid; sulphidopeptide (cysteinyl) leukotriene antagonists; LTB_4 receptor antagonists. The most studied groups are 5-lipoxygenase inhibitors and sulphidopeptide leukotriene antagonists. In Ukraine drug of the latter group - montelukast (e.g. Milukante) is registered [6, 7].

Many medical guidelines including the Global Initiative for Asthma (GINA), the PRACTALL (Practicing Allergology) Report on Asthma Treatment in Children, British Guideline on the Management of Asthma, Allergic Rhinitis and its Impact on Asthma (ARIA) recommend antileukotriene drugs as a means of effective controlling the course of the disease [2, 9].

According to unified clinical protocol of primary, secondary (specialized) medical care "Bronchial Asthma in Children" montelukast is used as monotherapy as an alternative to inhaled corticosteroids (ICS) in treating mild persistent BA and virus-induced wheezing in children with intermittent BA. It also may be prescribed additionally to ICS if the condition is not properly controlled.

Due to low parental commitment to basic therapy of BA the cases of uncontrolled clinical course of the disease become more and more common. In Ukraine there is some fear of using ICS and metered-dose inhalers (MDI). Thus, an alternative administration of montelukast (Milukante) orally once a day should contribute to a better control of the disease. In addition, even using paraclinical examination methods (spirometry and peakflowmetry) BA can be difficult to diagnose in young children. Therefore, they are recommended to use antileukotriene drugs as monotherapy for at least 6 weeks and if there is an adequate response to treatment – for 3 months.

The objective of the research was to analyze the effectiveness of antileukotriene drug montelukast as monotherapy in children with BA.

Materials and methods

There were examined 65 children with mild or moderate BA at the age of 5-7 years treated in the allergology department of the Ivano-Frankivsk Regional Children's Clinical Hospital (RCCH).

The prospective cohort study being a randomized open one was carried out considering parental awareness and informed consent, assessment of predictable risks and benefits according to Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki.

The diagnosis of BA was made, and the degrees of severity and appropriate basic therapy were determined according to the criteria approved by the Order of MH of Ukraine of October 08, 2013 No 868 "Unified clinical protocol of primary, secondary (specialized) medical care "Bronchial Asthma in Children" and GINA criteria (updated in 2015) [5, 8, 9].

All patients with acute exacerbation of moderate BA being treated in the allergology department received therapy according to "Step-3": medium and high doses of ICS and short-acting β2-adrenergic agonists, if necessary.

Patients of both groups received MDI salbutamol and fluticasone propionate (100-125 mcg 3 times a day) via the nebulizer or spacer. Patients of Group II received antileukotriene drug montelukast (Milukante – 1 tablet at night: the dosage for paediatric patients less than 6 years of age is 4 mg, over 6 years of age – 5 mg) additionally. Treatment outcomes were evaluated 2 weeks after the beginning of therapy (the exacerbation period). Being discharged from the hospital children of Group I received low-dose ICS monotherapy (50 mcg of fluticasone propionate twice a day via the spacer), and children of Group II received montelukast monotherapy (1 tablet at night; the dosage for paediatric patients less than 6 years of age is 4 mg, over 6 years of age – 5 mg) [3, 8, 10, 11].

The concentrations of total immunoglobulin E (IgE) and allergen-specific IgE were determined using the Hitachi Chemical Diagnostics chemiluminescent assay.

For daily monitoring of respiratory function peakflowmetry was performed using individual peak flow meters (Micro Medical Ltd, Great Britain). The peak expiratory flow (PEF), the average daily bronchial patency (ADBP) = $(PEF_{min} + PEF_{max}) \times 100\%/2PEF_{normal}$= ...% and the daily bronchial patency variability (DBPV) = $(PEF_{max} - PEF_{min}) \times 100\%/PEF_{max}$ = ...% were determined. The dynamics of these parameters during treatment was evaluated calculating an increase in ADBP: $ADBP_{after\ treatm} - ADBP_{before\ treatm}$ = ...% and a decrease in DPBV: $DBPV_{before\ treatm} - DBPV_{after\ treatm}$ = ...% [6].

Mathematical and statistical processing of the results was performed using a spreadsheet program Microsoft Excel for Windows. Normal distribution of data and equality of dispersions in samples being compared were proved before making calculations. Parametric criteria were calculated including the arithmetic mean of a sample (M) and the average error of the arithmetic mean (m); the Student's t-test was used to compare dependent samples after therapy. The difference was considered significant (two-sided) at $p < 0.05$.

Results and discussion

When analyzing anamnestic data there were recorded the cases of underdiagnosis of BA and accordingly inadequate treatment. In 60.0% of cases the first symptoms of asthma in children were triggered by acute respiratory viral infections (ARVI). It is important to note that in most young children ARVI was often complicated by wheezing (49.2%) and pneumonia (16.9%) which was rarely confirmed by chest X-ray. Unfortunately, most of these episodes were treated using antibacterial therapy despite normal values of the complete blood count and no infiltrative changes in the chest radiography. Nearly half of children were diagnosed with BA in the allergology department of the Ivano-Frankivsk RCCH after unsuccessful attempts of treating underdiagnosed pneumonia in district hospitals.

According to parents, sensitivity to indoor allergens was found to trigger disease in 6.45% of cases and sensitivity to chemical mediators when making the repairs in their apartments resulted in the manifestation of the disease in 7.5% of cases. Sometimes, asthma attacks occurred secondary to emotional stress. The onset of BA in healthy children was registered in 26.2% of cases.

The analysis of the child's feeding during the first year of life proved that breastfeeding for more than 6 month was rare. The severity of the disease was associated with lower rate of breastfeeding: in mild BA 23.8% of children were breastfed and in mild to moderate BA only 13.0% of children were breastfed. The obtained results suggested the dependence of BA on the method of feeding during the infant's first year of life.

When analyzing allergological anamnesis of patients other manifestations of atopy (atopic dermatitis, allergic rhinitis, pollinosis) as well as food and drug hypersensitivity were observed in 67.7% of cases. In addition, in mild to moderate BA combined allergic pathology was observed in 27.7% of cases.

In most cases the patient's condition during remission was unsatisfactory. Symptoms of BA included coughing episodes in 32.3% of cases, difficulty in breathing and/or chest tightness in 18.5% of cases indicating the absence of asthma control.

At admission to the hospital most children (69.2%) were diagnosed with moderate BA. During the initial examination tachypnea was registered in all children and tachycardia was observed in 84.5% of patients. It should be noted that psychoneurological symptoms including emotional lability (55.4%), headache (9.2%), urinary incontinence (1.5%), loss of appetite (43.1%), sleep disruption (60.0%) were often observed in children. 27.7% of children with BA complained of abdominal pain and when palpating the abdomen painfulness was observed in the epigastric area, the right hypochondrium, the periumbilical region and the Kehr's point. The above-mentioned symptoms may indicate functional gastrointestinal disorders (FGID) due to emotional lability as well as helminthic invasion often exacerbating symptoms of BA.

To diagnose impaired bronchial patency daily peakflowmetry was added to the complex of examinations (Table 1).

Table 1

Parameters of peakflowmetry at admission, M±m

Parameters	Control group (n=20)	Children with bronchial asthma (n=65)
Average daily bronchial patency, %	93.7±1.0	58.20±0.72*
Daily bronchial patency variability, %	4.60±0.41	29.31±0.71*

Notes: *- the probability of differences compared to the control group, p<0.001.

At admission to the hospital in all patients with BA the PEF reduced by 1.7-1.9 times compared to normal values (p<0.001).

An increased total IgE level was observed in most patients (86.2%).

The disappearance or reduction in main symptoms of the disease, recovery of motor activities in children or normalization of the parameters of daily peakflowmetry served as criteria for treatment efficacy and effectiveness.

The positive dynamics of clinical parameters during therapy was observed in all children. However, in patients receiving antileukotriene drug montelukast the improvement was registered 1-3 days earlier. On the 6^{th} -8^{th} day in Group I clinical stabilization of symptoms of the disease was observed in 61.9% vs. 81.0% in Group II (p<0.05). Subjective signs included improved sleep and appetite, reduced manifestations of asthenic syndrome and respiratory failure, the absence of recurrent asthma attacks. Objective criteria included the improvement of auscultatory findings: reduction in dry sibilant and buzzing rales, or their absence, normalization of breathing and heart rate. When assessing the values of peakflowmetry the PEF was found to be improved in all children (p<0.001), however, in children who additionally received montelukast better parameters of the ADBP were observed 77.29±1.17% vs. 72.87±0.73% in Group I (p<0.05). There was a similar tendency when assessing the increase in the ADBP 19.9±1.1% and 23.35±1.18% in Group I and Group II, respectively (Table 2). The DBPV reduced in all children after treatment, however there was no statistically significant difference between groups (p>0.05).

When analyzing the children's general physical and mental state 3 months after undergoing basic therapy we observed the lack of parental commitment to using ICS. Nearly half of patients (18 children) in Group I stopped basic therapy 1 (25.6%) and 2 months (20.5%) after the beginning of treatment. The remaining patients (21 children) took ICS irregularly. They reported periodical feeling of being unwell, difficult breathing and cough.

Table 2

Dynamics of parameters of peakflowmetry in children with BA during treatment, M±m

Parameters	ICS (Group I, n=39)		ICS+ montelukast (Group II, n=26)	
	before treatment	after treatment	before treatment	after treatment
Average daily bronchial patency, %	54.02±1.16	72.87±0.73*	53.94±0.82	77.29±1.17*#
Increase in the average daily bronchial patency during treatment, %		18.9±1.1		23.35±1.18#
Daily bronchial patency variability, %	31.97±1.57	19.32±0.28*	29.23±1.01	20.08±0.33*
Reduction in the daily bronchial patency variability during treatment, %		12.65±1.58		9.15±1.13

Notes:

1. *- the probability of differences between parameters before and after treatment, p<0.001;
2. #- the probability of differences between parameters of Group I та Group II, p<0.05

Patients of Group II received basic therapy every day. Only three of them (11.5%) stopped therapy 1 month after the beginning of treatment. When assessing the results of peakflowmetry 3months after undergoing basic therapy there were detected some differences between groups (Table 3).

Table 3

Dynamics of parameters of peakflowmetry in children with BA 3 months after undergoing basic therapy, M±m

Parameters	ICS (Group I, n=21)		Montelukast (Group II, n=23)	
	at the beginning of basic therapy	3 month after basic therapy	at the beginning of basic therapy	3 month after basic therapy
Average daily bronchial patency, %	76.94±0.82	81.29±1.17*	77.72±0.78	89.27±1.11*#
Daily bronchial patency variability, %	19.23±1.01	20.08±0.33*	20.03±1.38	18.83±0.24 *

Notes:

1. * - the probability of differences between parameters before and 3 months after treatment, p<0.001;
2. # - the probability of differences between parameters of Group I та Group II, p<0.05

The PEF parameters remained moderately reduced in most patients, however, in children who received montelukast the ADBP parameters were found to be higher 81.29±1.17% vs. 89.27±1.11% in Group I (p<0.05) and, accordingly, the assessment of general well-being was higher, too. In our opinion, such differences between groups are explained by the fact that patients

preferred taking montelukast to taking ICS, because only long-term continuous basic therapy according to the GINA guidelines has the positive effect.

Conclusions

1. The problem of underdiagnosis of BA remains relevant to both our region and Ukraine in general.

2. In 60.0% of cases the first symptoms of asthma in children were triggered by ARVI.

3. The use of antileukotriene drug montelukast (Milukante) contributes to the reduction in the manifestation of the main symptoms (asthma attacks, respiratory failure, cough), positive dynamics of the parameters of peakflowmetry, normalization of the child's overall wellbeing over a short period of time.

4. There was noted that patients preferred long-term use of antileukotriene drugs to taking ICS (88.5% vs. 53.8% of cases, respectively).

Prospects for further research

Prospects for further research include the analysis of the effectiveness of long-term combination basic therapy (ICS and montelukast) in children with moderate BA compared to monotherapy with ICS.

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