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INFLUENCE OF MONTELUKAST ON EXERCISE-INDUCED ASTHMA

SUMMARY

Among specific forms of asthma, exercise-induced asthma (EIA) is the most common. One of the most important factors released in this form of asthma is leukotriens. The place and role of leukotrien modifiers in treating EIA is still not clearly defined. Ten children 5-15 years of age were included in this study. We followed up different lung parameters in children exposed to exertion before and after montelukast by using spirometry. All children included in the study were submitted to the prick test. Results obtained in our study showed that montelukast statistically significantly reduced lung parameters on exertion, when compared with the results obtained before it. Montelukast did not completely block EIA.

Key words: **exercise-induced asthma, leukotrienes, montelukast**

INTRODUCTION

Asthma is a chronic inflammation in which many cells play an important role, including mastocytes, eosinophils, T-lymphocytes and epithelial cells. Two basic responses of the immune system to infection are Th1 and Th2. In allergic asthma with an early onset, Th2 response is favourized due to a changed genetic basis in asthmatics (1, 2).

Classifaction of Asthma According to the Factor Leading to an Attack. According to the factor leading to an asthmatic attack, asthma can be devided into classic and specific asthma. The classic asthmatic attack is characterized by asthma symptoms, but without finding out its real cause. Of specific forms, aspirin sensitive asthma and psychogenic asthma rarely occur in children; hay fever asthma appears more often, but exercise-induced asthma (EIA) is the most frequent.

Exercise Induced Asthma. This type of asthma occurs in 70-80% of children having the disease. Sometimes, it occurs during physical exercise, but more often it appears 5-7 minutes after the exercise, and the symptoms gradually disappear within 60 minutes. Bronchodilatation, whose cause is still being sought for, develops most frequently during and immediately after the exercise. The cause of this type of asthma is still unknown, but it is supposed that, due to the exercise, airways cool and dry, which leads to a release of diferent mediators, especially cysteinil leukotriene (LTC4, LTD4 and LTE4). These mediators play the most important part in occurring of EIA. Other mechanisms, which participate in cooling, are most probably a reflex

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pathway and reactive hyperemia. However, the most reliable theory today claims that the release of mediators in cooling and drying are provoked by the change of osmolarity of periciliary liquid. By increasing the osmolarity of periciliary liquid, the influx of sodium and chlorine occurs, and Ca in the cell follows, which activates phospholipase A and production of arachidonic acid, whose further disintegration induces the creation of leukotriene (3-10).

Biosynthesis of Leukotriene, the Place of Their Creation and Mechanisms of Their Activity. Leukotrienes, as one of the most important mediators in asthma, were discovered in 1960 by Broklerhurst and were given the name of a slowly reacting substance – anaphylaxis (11). They are created by disintegration of the phospholipid membrane of mast cells, eosinophils and some other cells through 5LO (12, 13). Their creation is initiated by the effect of some foreign material, antigen virus etc, which activate phospholipase, which disintegrates phospholipids to arachidonic acid. The most potent of all leukotrienes is LTD4 (14). The most important cells in creating of leukotrienes in the lungs are mast cells, basophils, eosinophils etc. Mast cells and eosinophils are the rich source of LTC4, while neutrophils and alveolar macrophages are the source of LTB4. Cysteinyl leukotrienes provoke bronchoconstriction in the body, vasodilatation and increased vascular permeability, chemotaxis, remodeling of bronchial walls. They also affect non-myelinated C nerve fibers. LTB stimulates chemotaxis of the neutrophils, contact of neutrophils and endothelial cells and activation of neutrophils and release mediator enzymes. Besides, LTB4 stimulates the production of interleukin 6 and other IL by monocytes. Leukotrienes achieve their effect through leukotriene receptors (15, 16). There are two kinds of leukotriene receptors in the body (17) - CLR and BLR. Cys-leukotriene receptors can be divided into three groups. The first group of receptors, which are the most important for the presenting of asthma symptoms, are localized in the smooth muscles of bronchi and macrophages. According to the latest studies, there are also two groups of BLT receptors (18). The genes for the two receptors are on the 14^{th} chromosome. They were discovered by the fact that the same antagonist of BLT receptors do not act on them.

Leukotriene Modifiers. Some time ago, a new group of drugs for treating asthma was produced. The way these drugs act is a combination of anti-inflammatory and bronchodilatatory action (19). During the work on the drugs used in the treatment of asthma before the knowledge of leukotriene modifiers, it was established that inhalatory corticosteroids do not affect the production of leukotrienes (20, 21). This led to the necessity to introduce a new group of drugs, which block either synthesis or effect of leukotrienes. Thus, two groups of leukotriene modifiers were developed. The first group consists of those blocking the synthesis of leukotrienes, the main representative being zileuton, and the second group comprises drugs that block leukotriene receptors. This group includes zafirlukast, montelukast and pranlukast etc (22-28).

AIMS

The aim of our study was to establish whether montelukast reduces sensibility of the bronchial tree on exertion in children suffering from EIA.

MATERIAL AND METHODS

Ten children of both genders, 5-15 years old, suffering from EIA were included in the study conducted according to the GINE criteria. Parents' approval was obtained prior to the participation of their children in the study. Diagnoses were established on the basis of:

1. Anamnesis and questionnaire
2. Clinical examination
3. Lung functional tests – spirometry
4. Provocation test on exertion
5. Dermatological prick-test

1) On the bases of anamnesis and enquiry that comprises the commonest questions related to asthma, mild persistent asthma can be diagnosed. Clinical examination will contribute to anamnesis and further establishing of asthma diagnosis. In the course of the clinical examination the lung auscultation was done, as well as an X-ray, if needed, and the measuring of height and weight.

2) The examination of the lung functions was carried out by spirometry (Erich Jaeger, Masterscope PC-Dell). During examination, the lung parameters FVC, FEV_1, VC were monitored. Based on the flow/volume curve, which represents a graphic presentation of the relationship between the maximal curve of the flow and the volume of air, dynamic lung parameters were followed up. On the expiratory part of the curve, the peak expiratory flow rate was observed (PEF) and the maximal expiratory flow between 25% and 75% of the vital capacity.

3) The exercise testing was carried out by an ergo-bicycle (Ergometrics er900). Exertion was measured on the basis of the heart frequency, which

reached, during the testing, 80% of the value for the age group maximum. The sub-maximal exertion was counted as the heart frequency of 220 minus the number of the child's age. The beginning of the subjective complaints in a child, that is a fall of FEV_1 by more than 15%, was the moment to stop the test. The spirometric examination was carried out immediately before and after the exertion, until normalization of FEV_1.

4) Dermatologic prick tests were carried out on inhalatory allergens in the way that on the inner part of the forearm, previously cleansed with alcohol, a drop of allergen was put, each prick at the distance of two centimeters. The pricks were done at the angle of 45 degrees with a lancet. A positive probe with histamine and a negative probe with sodium chloride were performed. The reaction of the early hyperresponsiveness was interpreted 15 – 20 minutes later.

All the children included in the study were submitted to dermatological test first, on the basis of which atopy was proved. Positive atopy plus a positive exertion test is a proof that children have EIA. The therapy was excluded 2 – 4 days before the beginning of the experiment using antihistamines, and seven days earlier compared to the children on prophylaxis with ketotifen. The study included 10 children of both genders 10 – 15 years of age. The children in the group controlled themselves. Before the exercise, the initial spirometry was done. Only the children having FEV_1 higher than 65% were included in the study. The test was done at room temperature and humidity of 40%. After a mild warming up, the children rode ergo-bicycles for six minutes until a sub-maximal exertion was reached. During the 1^{st}, 7^{th}, 15^{th} and 30^{th} minutes after the exercise, the following parameters were noted down: (FEV_1, VC, FVC, PEF, FEF_{25} and FEF_{50}). Having finished the test, the children were given 5 mg tablets of montelukast. After 24 hours, ergo tests were performed again in the aforementioned way. The spirometric measuring was carried out at the same intervals as above. After each spirometry the same parameters of the lung functions of the previous day were measured. The obtained results from the first and the second day were compared.

RESULTS

Ten children were included in the study, being submitted to the exertion tests. The basic characteristics and anthropometric indicators are presented in table 1, and the indicators of the lung function at rest are shown in table 2.

Table 1. Anthropometric indicators in asthmatic children induced by exertion (body weight and height, age)

	X±SD	MIN.	MAX.
GS	12.4±4.64	8	15
Tt	44.5±23.07	21	65
Tv	158±79.26	130	180

Table 2. Indicators of the lung function at rest in asthmatic children induced by exertion

	X±SD
FVC	84.19±13.27
FEV_1	91.37±11.03
PEF	73.08±11.08
FEF_{25}	73.99±9.71
FEF_{50}	74.92±6.89

Out of the children analyzed, 6 of them were boys (60%), and 4 girls (40%), 5–15 of age. In the final analysis of data, we included the children who endured sub-maximal exertion and responded to it with a significant increase in the resistance of distal bronchi. The characteristic response to exertion is presented in figures 1 and 2.

As can be seen in figures 1 and 2, seven minutes after riding bicycles, there was a significant fall in FEV_1 and FEV_{25}. After 15 minutes, particularly after 30 minutes of the parameters' follow up, they partly returned to the initial values. When exertion was repeated the following day with the previous administration of montelukast, significant variations in these parameters were not noticed. In the seventh minute after the exertion, FEV_1 decreases to a significant degree, from 84.3%

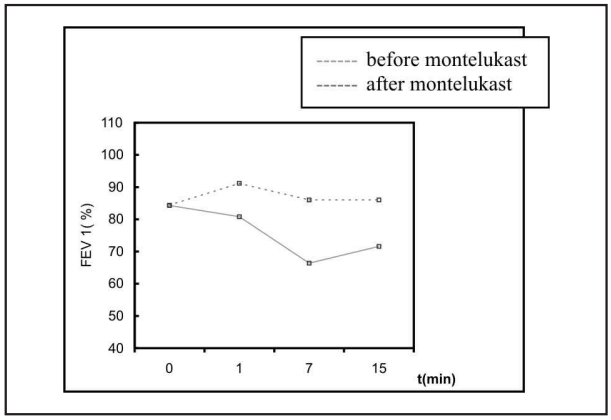

Figure 1. Graphic analyses of the change in FEV_1 on exertion before and after montelukast in the characteristic patient

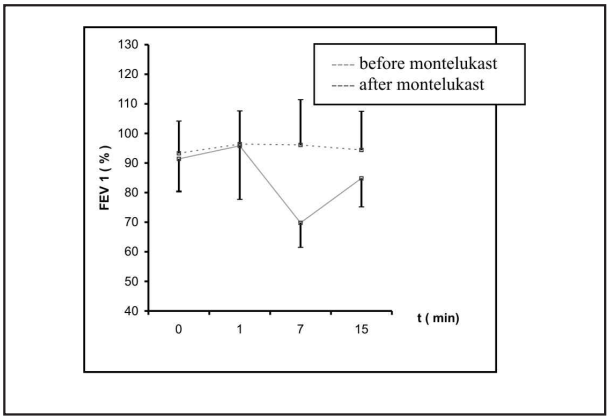

Figure 2. The average values of FEV_1 as a response to exertion before and after montelukast in asthmatic children

to 66,4%, while after montelukast being administered, a decrease of FEV_1 was not registered when compared to the initial values, (from 84.4% to 86%). We got similar results when we followed up FEF_{25}. In the seventh minute after the exertion, FEF_{25} decreases to a significant degree, from 79.7% to 51%, while after montelukast, the flow improved in the seventh minute after the exertion – 97.4% (the initial values were 83.9%). Figure 2 shows the average values of FEV_1 before and after the exercise with and without montelukast. As it can bee seen on the figures, sub-maximal exertion led to a significant decrease in these parameters in the seventh minute, when the compared values were statistically significant ($p<0,01$).

The obtained difference in the average value of FEV1 at the beginning and during the first minute after the exertion does not show any statistical difference. From 91.37%, FEV_1 increased to 95.79% ($t=1.083$; $p>0.05$) after the exercise, and it significantly decreased to 69.84% in the seventh minute ($t=9.189$; $p<0.01$). After 15 minutes, FEV_1 does not go back to the initial values 84.82% ($t=2.978$; $p<0.01$). Only after 30 minutes, FEV_1 returns to the initial values. The obtained differences in FEV_1 with montelukast, and after the exertion, were tested in the same way as previously. The initial value of 93.26% increased after the exercise to 96.40% and did not significantly change during the test: in the seventh minute it reached 96.08%, and in the fifteenth minute 94.44%. We also followed the average value of FVC and PEF in our patients. The average values of FVC on exertion were initially 84.19%, but immediately after the exertion they were 84.36%. Seven minutes after the exercise test, FVC significantly decreased to 72.18%, and in the fifteenth minute it began to return to the initial values. (80.97%). However, when the sub-maximal exertion was repeated 24 hours after montelukast administration, the FVC values did not significantly vary when compared to the initial values (85.80). Immediately after the exertion, the value in the seventh minute was 86.31%, 88.32% and in the fifteenth minute 84.04%. Statistically significant difference between FVC at the start and in the seventh minute ($t=1.149$; $p>0.05$) was not found. At rest, the average value of PEF was 77.50%, immediately after the exertion 76.45 %, and in the seventh minute it decreased to 60,1% and at the fifteenth raised to 67,90%. This decrease in the seventh minute is statistically significant when compared with the initial value ($t=4.612$; $p<0.01$). Dynamic changes of PEF during the maximal exertion after montelukast were significantly different when compared with the state before drug intake. From the initial 73.37% after the exertion, PEF increased to 80.27, during the seven minute of the exercise it kept the high level of 78.67%, and did not change much after 15 minutes (77.41%).

The average value of FVC at the beginning of the study was 84.2% +13.3 (X+SD). During the first minute after the exercise it was 84.4% ±16.7%, and during the seventh minute 72.2% ± 9.7 %. Fifteen minutes after the beginning, the value approached the initial one – 80.97% ± 12.9%. Statistically significant decrease was noted in the seventh minute after the exertion, when compared with the initial value ($t= 6.152$; $p<0,01$) for $n=10$. After montelukast administration, variations in FVC were not statistically significant during the test.

The average value of PEF after the initial measurement was 77.5% ± 11.8%. It significantly changed during the seventh minute after the exertion 60.1±14.4 ($t=3.092$; $p<0.01$), but even after 15 minutes, it was still low, 67.9% ± 10.8% ($t=3.092$; $p< 0.01$). After montelukast, PEF did not decrease, but it increased during the first minute to 80.3% ± 14.0%, and in the seventh minute to 78.7% ± 12.3%. At the beginning of the study, the average value of FEV_1 was 91.4% ± 11.0%. In the first minute after the exertion it increased to 95.8% ± 18,1%, and in the seventh minute it significantly decreased to 69.8% ± 8.3% ($t=6.865$; $p<0.01$) for $n=10$. Variation in FEV_1 after montelukast administration was insignificant. It varied from 93.3% ± 10.9% at the beginning, to 96.4% ± 11.2% in the first minute and 96.1% ± 15.3% in the seventh minute. In all the children, there was a significant decrease in FEV_1 (> 15%, table 1), while after montelukast the values did not significantly change, in some cases they even increased (table 2). In figure 3, individual values of FEV_1 after a maximal response induced by the exertion are presented.

In all the children, there was a significant decrease in FEV1 before montelukast when compared to the state after montelukast administration. The obtained difference in the average values of

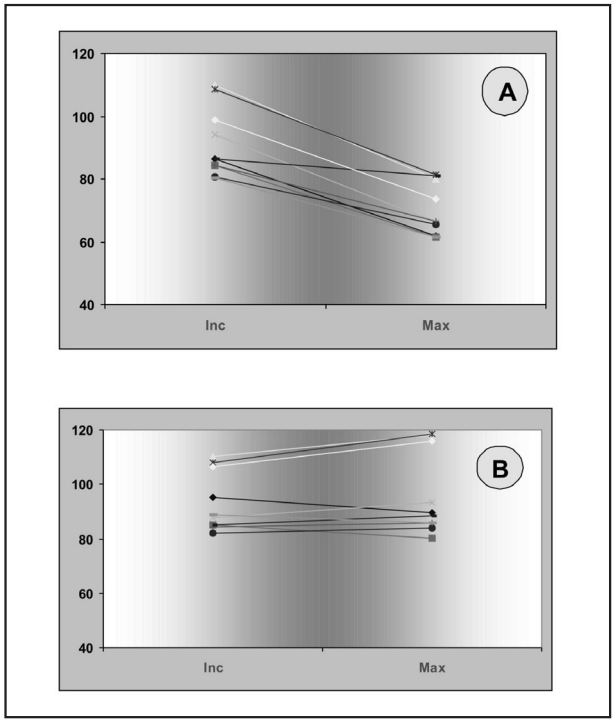

Figure 3. Individual cases of FEV1 changes after a sub-maximal exertion before and after montelukast in asthmatic children

FEF_{25} in the first (73.9% ± 9.71%) and seventh minute (52.3 ± 13.8%) after the exertion was statistically significant (t=4.482; p<0.01). With montelukast, there was not any decrease in the initial values (79.36% ± 12.6%), but the flow was improved. Seven minutes after the exertion, it mounted (80.6% ± 11.9%), and 15 minutes after the test, it was 81.72% ± 11.5%; t=-0.432; p>0.05 for n=10. The changes in the flow in small airways after the exertion are presented in figure 4.

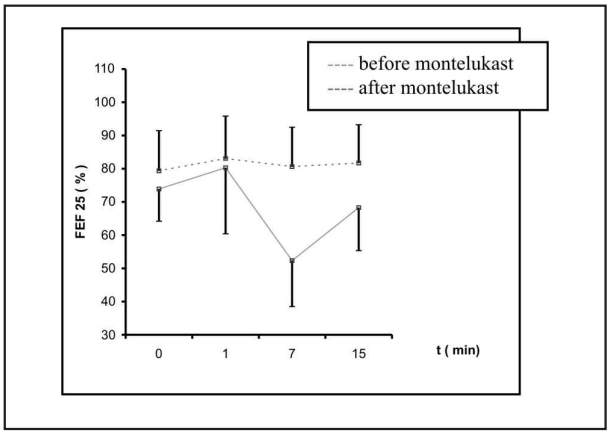

Figure 4. Average values of FEF_{25} as a response to the exertion before and after montelukast in asthmatic children

The average initial value of FEF_{25} was 73.9% ± 9.7%. In the first minute, it increased to 80.3% and in the seventh minute it decreased to 52.3%. In the fifteenth minute the flow improved and approached the initial value and was 68,3%. Statistically significant difference was found when compared with the initial values in the seventh minute after the exertion (t=4.482; p<0.01). After montelukast and exertion, however, the flow values in small bronchi FEF_{25} did not show any significant variation. From the initial 79.4% after the first minute, they increased to 83.1% and were at the same level during the test. In the seventh minute they were 80.6% and at the fifteenth minute 81.7% (t=-0.432; p>0.05). The upper respiratory disease and the number of attacks per year are important anamnestic risk factors for development of asthma in children. Taking this into account, we wanted to see whether there was a significant statistical difference between the average medium values of FEV_1 24 hours after the effect of montelukast related to the presence or absence of the aforementioned risk factors. Of ten children included in our study, nine (90%) had upper airways disease, and only one (10%) did not have it. The average medium value of FEV_1 in children who had an additional upper airways disease was 89.50%, and in children without some other disease it was 96.81%. Differences were compared by the use of the Student's t-test for independent samples. No statistically significant differences were found (t=0,433; p>0.05). As to the number of attacks per year, it was interesting to establish whether the children having five or more attack per year had a different average value of FEV_1 24 hours after montelukast when compared to those having less than 5 attacks. Out of ten children included in the group, 5 had more than 5 attacks, and the number of attacks in other 5 was less than 5. The average value of FEV_1 in children having less than 5 attacks was 95,18%, and in those having more attacks, it was 96,98%. The noted difference was compared by the Student's t-test for independent samples. Statistically significant difference was not found (t=0.176; p>0.05).

DISCUSSION

In our study, we have started from the fact that, today, leukotrienes are one of the most important mediators of an early phase of bronchial obstruction appearing after 15 minutes and lasting two to three hours. These mediators play an important role even in the late phase, but not as important as they do in the early phase. The role of inhibitors in treating asthma has not been defined yet and, in guidelines for treating asthma, they are mentioned only superficially, mainly as the therapy for treating aspirin-induced asthma. The aim of our study was to

prove that the inhibitor of leukotriene, montelukast, improves the lung parameters in exercised – induced asthma. We have decided to study the role of montelukast in EIA due to the fact that cysteinyl leukotrienes are among the most important mediators, which release into EIA (3). Today, as a choice for treating EIA, the long-lasting beta agonists are mentioned in the literature (13, 14). There are more and more studies which emphasize the role of leukotriene modifiers in the prevention of this type of asthma. Its advantage, in comparison with the long-lasting beta agonists, in the first place, is the fact that their role is anti-inflammatory and do not develop tachyphylaxis after a longer intake.

The results of our study which included ten children are obtained on the basis of the following parameters: FEV_1 and FEF_{25} in the characteristic patient, then, FEV_1, FVC and FEF_{25} during the experiment, and, in the end, changes in individual values. The basic parameter of the lung function improves to a significant degree after montelukast when compared to the previous values. The obtained average values, however, are lower than the average values before testing. This points to the fact that montelukast shows different reactions and that, in the average, does not block EIA. There are many disputes in the literature over the role of montelukast and other leukotriene modifiers in treating this type of asthma and differences in the action of long-lasting beta agonists and leukotriene modifiers on the bronchial tree (22-28). These disputes may be reduced to the influence of study design on the obtained results, but still there are no proofs which drug is more efficient. LEF and others established an improvement of the FEV_1 value by 47%. Their study has similar results as ours, but the children were followed up for 12 weeks. They say that the effect of the drug was not the same in all the children. Kemp and others included in their study 27 children aged 5 to 15 with the values of FEV_1 over 70%. Montelukast was being administered to children in duration of two days, and provocation with the exertion was performed at the beginning and 24 hours after the last doze. The result showed that montelukast reduced decreasing of FEV_1 value by 30% when compared to the values before drug intake and on placebo, but it did not block completely EIA. Pearlman and others presented similar results in their study, but only with zafirlukast. McFadden and others underlined that, besides the improvement of FEV_1 function after montelukast, when compared to the values after placebo was administered, there was still a decrease in FEV_1 value by 20% when compared to the values before the exertion, which represented a positive result.

Our results mainly coincide with the results of the aforementioned studies. Montelukast reduces AIBH and, as a drug, has its place in the treatment of this type of asthma. In most children it blocks partially or completely the decrease of FEV_1 values and other parameters on the exertion. Additionally, multi-centric studies are necessary, in which montelukast along with other drugs will be included in the treatment of this type of asthma in order to establish its definite position in treating this disease.

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UTICAJ MONTELUKASTA NA ASTMU IZAZVANU NAPOROM

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SAŽETAK

Astma izazvana naporom jedna je od najčešćih formi specifičnih astmi. Jedan od najznačajnijih faktora koji učestvuje u patofiziologiji ovog oblika astme jeste leukotrijen. Uloga inhibitora leukotrijena u tretmanu ovog oblika astme još uvijek nije u potpunosti definisan.

U studiju je uključeno desetoro djece uzrasta od 5 do 15 godina. Praćeni su parametri plućne funkcije (spirometrija). Djeca su izlagana naporu prije i poslije upotrebe montelukasta, a nakon toga im je rađena spirometrija. Svim ispitanicima rađen je kozni prick test.

Rezultati pokazuju da montelukast statistički značajno smanjuje pad parametara respiratorne funkcije kod ispitanika nakon napora u odnosu na parametre koji su registrovani nakon napora bez upotrebe montelukasta.

Montelukast ne blokira u potpunosti astmu izazvanu naporom.

Ključne reči: **astma izazvana naporom, leukotrieni, montelukast**