

Change of Bronchial Hyperresponsiveness in Asthmatic Children

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SUMMARY

Introduction Bronchial hyperresponsiveness (BHR) is a factor in predicting bronchial asthma independently of inflammation markers.

Objective The aims were to determine the frequency and important predictive facts of BHR and the effect of prophylaxis by Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program (NAEPP) on BHR in asthmatic children.

Methods BHR in 106 children was evaluated by the bronchoprovocation test with methacholine.

Results The prevalence rate of symptomatic BHR is 18% for crucial point of PC20=4.1±3.03 mg/ml and PD20=3.22±2.59 µmol methacholine. On average asthmatic children express moderate BHR, which persists even two years after administering prophylaxis. After two years bronchial reactivity is significantly smaller, the change of FEV₁ is significantly smaller, the velocity of change of slope dose response curve (sDRC) is faster and the provocative concentration of methacholine that causes wheezing is 2-3 times lower. A mild sDRC shows milder bronchoconstriction after two years. The fast change of bronchial reactivity in 41% of asthmatic children is contributed to aero-pollution with sulfur dioxide and/or, possible insufficient and/or inadequate treatment during two years of administering prophylaxis. A simultaneous effect of allergens from home environment and grass and tree pollens and of excessive aero-pollution on children's airways is important in the onset of symptomatic BHR. After two years of treatment by GINA and NAEPP children do not show asthma symptoms or show mild asthma symptoms, however bronchial sensitivity remains unchanged.

Conclusion Optimal duration of anti-inflammatory treatment in asthmatic children who show moderate bronchial hyperresponsiveness should be longer than two years.

Keywords: bronchial hyperresponsiveness; children; asthma

INTRODUCTION

Bronchial hyperresponsiveness (BHR) is a condition of excessive airway irritability and the factor in predicting bronchial asthma independently of inflammation markers. BHR in asthmatic children is a consequence of chronic immunologic inflammation with stimulative tendency of developing bronchial obstruction during a response to different stimuli. An appropriate procedure to verify bronchial hyperresponsiveness in children is a bronchoprovocation test with methacholine. There is a huge causality between the clinical difficulty of bronchial asthma with applied medications on one side and BHR on the other.

The treatment of bronchial asthma aims at enabling the child to engage in normal everyday activities, more exactly to be involved in physical activities and sport without restrictions. The therapy of bronchial asthma should relieve the child of respiratory discomforts during the day and night, enabling attendance of nursery or school. Moreover, its purpose is to establish a normal lung function with low daily variations of peak expiratory flow (PEF), as well as adequate bronchial responsiveness. The most effective medications for treatment of childhood asthma are inhaled corticosteroids,

which are the first line of therapy in children who suffer from severe persistent and moderately persistent asthma. The recommended therapy by the British Guidelines [1] and a number of authors such as Nielsen and Bisgaard [2] recommend for children who suffer from severe persistent asthma high doses of inhaled corticosteroids (800-2000 µg of beclomethasone dipropionate per day), long-acting bronchodilators, sustained-release theophylline, long-term use of oral corticosteroids, urgent application of quick-relief medications, such as inhaled short-acting β₂-agonist and application of immunomodulators.

Children who suffer from severe refractory steroid depended asthma and steroid independent asthma have poor response to usual conventional therapy and demand a long-lasting use of medications with anti-inflammatory and immunomodulatory effects, and according to Rabinovitch et al. [3] intake of immunoglobulin G.

OBJECTIVE

The aims of our study were to determine the frequency and important predictive facts on BHR and the effect of prophylaxis by GINA

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(Global Initiative for Asthma) [4] and NAEPP (National Asthma Education and Prevention Program) [5] on BHR in children who suffer from asthma.

METHODS

In our study BHR was evaluated by a bronchoprovocation test with methacholine and a modified Cockcroft protocol [6]. We used methacholine chloride powder for inhalation (Methapharm®, Canada), a spirometer (Jaeger Master Scope®) and a compressed nebuliser with corresponding aerosol flow and the size of particles. A bronchoprovocation test with methacholine was done in 2006 and was repeated two years later, in 2008. In the study 106 children aged 10 years were randomly selected from general paediatric population. Based on exclusion criteria ten children were eliminated, and the final studied group involved 96 children. Including criteria for asthmatic children were determined based on the GINA guidelines and accordingly the excluding criterions.

A statistical analysis was carried out by ANOVA one-factor and two-factor analysis of results, using the program SPSS. Data were obtained at the 5% significance level with 90% certainty, assuming on 2 SD. Time was included as a descriptive parameter and the analysis of covariance was used. The estimate of the significance of difference was performed by Pearson test, Fisher test, Kruskal–Wallis test, Student t-test, Mann–Whitney U-test, Wilcoxon Rank Sum W-test and Spearman's coefficient of correlation with regression analysis.

RESULTS

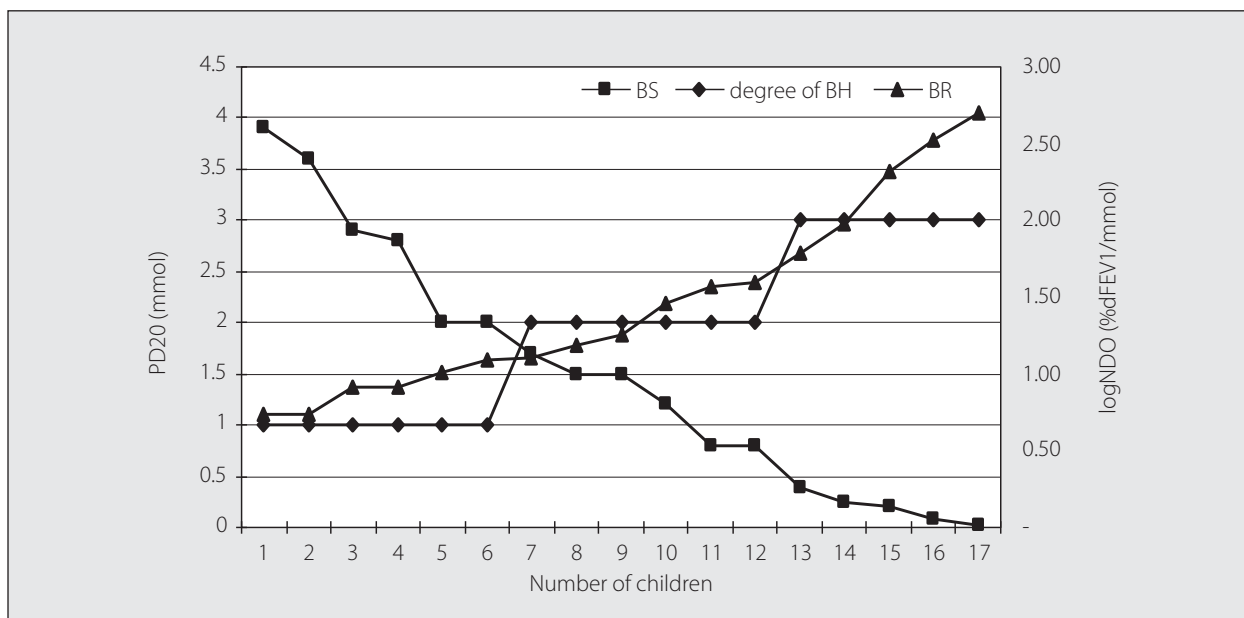
Of 96 studied children, BHR was revealed in 21 (22%) of whom 17 children (18%) had bronchial asthma. In the asth-

matic children, atopic and non-atopic, we repeated bronchoprovocation test with methacholine after administering prophylaxis. The results are shown in Graphs 1, 2, 3 and 4.

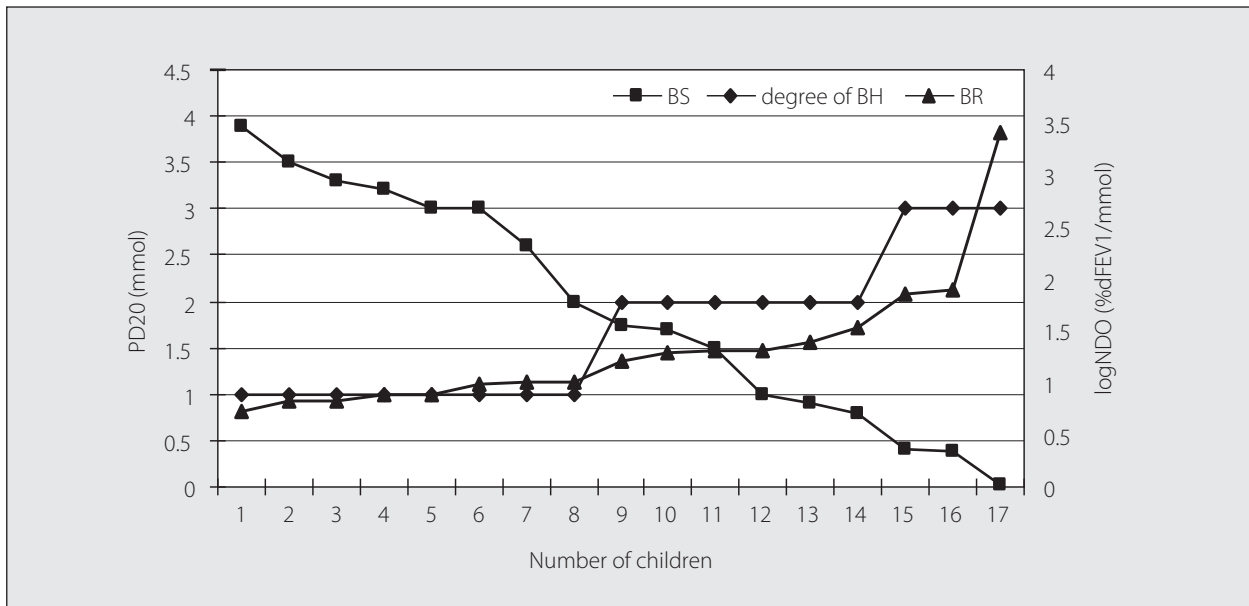
In the 17 asthmatic children who underwent the bronchoprovocation test with methacholine in 2006 we found that the average value of provocation dose of methacholine that caused a 20% fall in the FEV1 with initial value (PD20) which was 1.51 ± 1.23 μ mol of methacholine; the average value of provocation concentration of methacholine (PC20) was 1.66 ± 1.52 mg/ml, and the average value of provocation concentration of methacholine causing wheezing (PCw) was 1.66 ± 1.52 mg/ml methacholine, which corresponded to the fall of FEV1 for $35 \pm 14\%$ on average, with an average slope of dose response curve for 83 ± 139 , and to a logarithmic value of slope of dose response curve of 1.46 ± 0.61 .

In June, 2008, we repeated a bronchoprovocation test with methacholine in the same group of children, and we found average PD20 of 1.94 ± 1.24 μ mol methacholine, average PC20 of 2.18 ± 1.37 mg/ml methacholine and average PCw of 0.60 ± 0.61 mg/ml methacholine, which corresponded to a fall in the FEV1 on average for $26 \pm 6\%$, to average slope dose response curve for 165 ± 593 and to logarithmic value of slope dose response curve for 1.31 ± 0.64 .

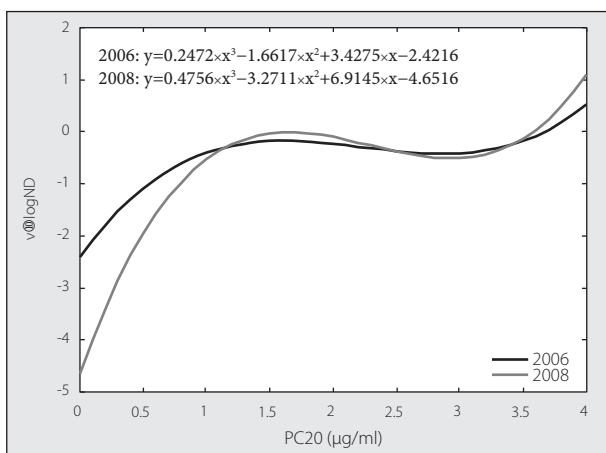
Bronchial sensitivity in asthmatic children, in other words, the provocation dose of methacholine (PD20) that causes a 20 per cent fall in the FEV1 as the provocation concentration of methacholine (PC20) that caused a 20 per cent and more fall in the FEV1 was approximately the same regardless of the year when the bronchoprovocation test was performed (Pearsons' coefficient of correlation $r=0.7920$, $p=0.000$; Pearsons' coefficient of correlation $r=0.8794$, $p=0.000$). Bronchial reactivity in asthmatic children, in other words the logarithmic value of slope dose response curve ($\log\text{SDR}=\%d\text{FEV1}/\mu\text{mol}$) was on average significantly lower in 2008 (1.31 ± 0.64) than in 2006 (1.46 ± 0.61) for a given threshold of bronchial response (Pearsons' coefficient correlation $r=0.4625$, $p=0.062$). In



Graph 1. Bronchial sensitivity (BS) and bronchial reactivity (BR) in regard to the degree of bronchial hyperresponsiveness (BH) in asthmatic children in 2006



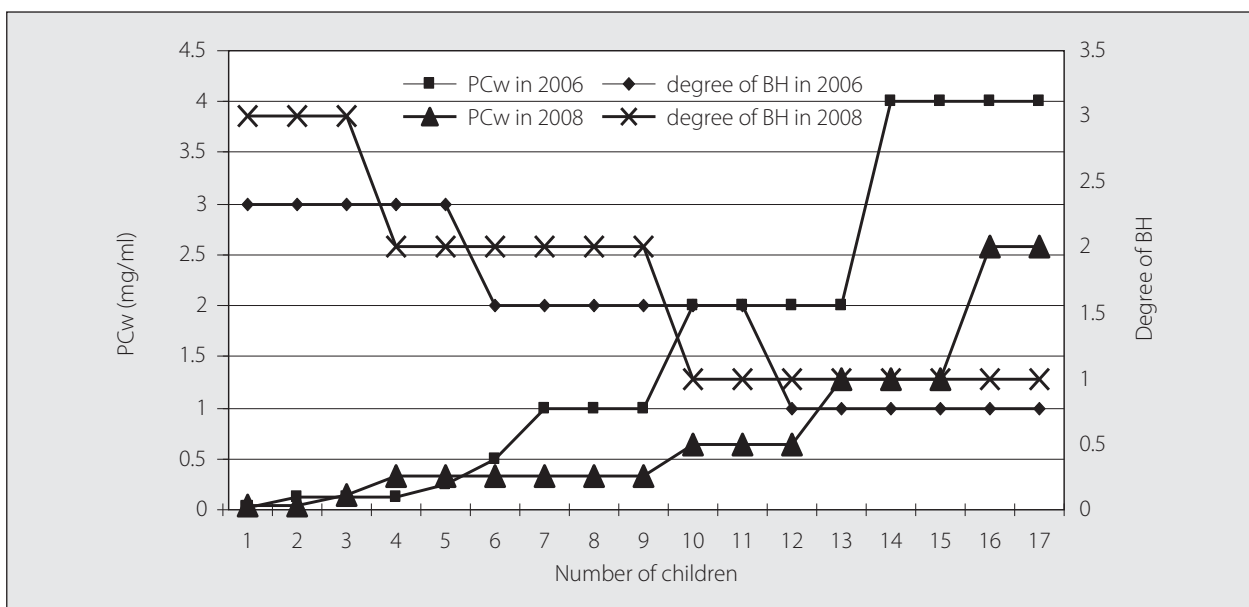
Graph 2. Bronchial sensitivity (BS) and bronchial reactivity (BR) in regard to the degree of bronchial hyperresponsiveness (BH) in asthmatic children in 2008



Graph 3. The velocity of change of slope dose response curve in asthmatic children in 2006 and 2008

2006, bronchial reactivity was low ($\log\text{SDR} < 1.1$) in six children (6%), whereas in 2008 it was low in 10 children (10%) ($\log\text{SDR} < 1.3$). The change of FEV1 rate (%dFEV1) was significantly lower in asthmatic children in 2008, meaning that the correlation between the values of %dFEV1 in 2006 and 2008 were relatively low (Pearson's coefficient of correlation $r = 0.2944$, $p = 0.251$). The results are shown in Graphs 1, 2 and 3.

The velocity of change of slope dose response curve ($\sigma @ \log\text{SDR}$) in the asthmatic children was obtained by a mathematic extrapolation of the results, as shown in graph 3. In the asthmatic children the velocity of change of slope dose response curve was faster in 2008 than in 2006. The velocity of logarithm of slope of dose response curve for every PC20 in 1996 was calculated using the formula: $\sigma @ \log\text{SDR} = 0.2472 \times \text{PC}20^3 - 1.6617 \times \text{PC}20^2 + 3.4275$



Graph 4. Relation between PCw and degree of bronchial hyperresponsiveness (BH) in asthmatic children in 2006 and 2008

$\times PC20 - 2.4216$, and in 2008 it was calculated by using the formula: $\sigma \log SDR = 0.4756 \times PC203 - 3.2711 \times PC202 + 6.9145 \times PC20 - 4.6516$.

The appropriate slopes of dose response curve (83 ± 139 ; 165 ± 593) and the appropriate values of PD20 (1.51 ± 1.23 μmol ; 1.94 ± 1.24 μmol , respectively) in relation to the crucial point of $PD20 \leq 3.99$ μmol methacholine showed moderate bronchial hyperresponsiveness in the majority of the asthmatic children, regardless of the year when the study was conducted. In children that showed moderate and severe bronchial hyperresponsiveness, elevated bronchial sensitivity to methacholine ($PD20 \leq 1.7$ μmol ; $PD20 \leq 1.5$ μmol) was promptly followed by elevated bronchial reactivity to methacholine ($\log SDR \geq 1.1$; $\log SDR \geq 1.3$), regardless of the year when bronchial responsiveness was measured. The bronchial reactivity measured in 2008 was significantly fast in six asthmatic children (6%).

The provocative concentration of methacholine that caused wheezing (PCw) in the asthmatic children was 2 to 3 times more favourable in 2008 (1.66 ± 1.51 mg/ml) than in 2006 (0.60 ± 0.61 mg/ml), and there was a slight correlation between the mentioned values of PCw (Pearson's coefficient correlation $r = 0.3731$, $p = 0.140$). The results are shown in Graph 4.

The bronchoprovocation test with methacholine in the asthmatic children was concluded by the use of bronchodilator (salbutamol). During 2006 study period, in asthmatic children the bronchodilator response ($+20\%$ FEV1) lasted 19 ± 8 minutes, whereas in 2008 the bronchodilator response was slightly faster (13 ± 5 minutes) and with a significant correlation (Pears' coefficient correlation $r = 0.6883$, $p = 0.002$).

Thanks to our colleagues from the Public Health Institute in Kragujevac, during 2006 and 2008 we received data on the average quantity of the total disposed waste, pollutants, sulfur dioxide (SO₂) and soot. We did not have any data on the concentration of nitric dioxide due to the fact that there were no measurements taken in our area. We obtained data by the beginning of 2001 and by the end of 2008 after having completed our research and we can accept them only as a supplement to the discussion of our results.

Air-pollutants from the deposited waste (859 mg/m² per day) exceeded the allowed upper limit mostly in the centre of the city, i.e. the location of the school where we carried out our first study in the period of June, 2006. In the second study period of June 2008, the quantity of total deposited waste was 2.5 times lower (339 mg/m² per day) than in the same month two years earlier.

The upper limit of SO₂ concentration was 150 $\mu\text{g}/\text{m}^3$ per day. In June 2006, the average monthly value (amv or av/m.) of SO₂ was 32 $\mu\text{g}/\text{m}^3$ per day exceeding the upper limit of SO₂ during one day (195 $\mu\text{g}/\text{m}^3$ per day). Two years later, we repeated the bronchoprovocation test and measured aero-pollution in the centre of the city. In June 2008, the average monthly value of SO₂ was 3.4 times higher than in June 2006, reaching 108 $\mu\text{g}/\text{m}^3$ per day. The upper limit of SO₂ was exceeded during four days, with a maximum value of 165 $\mu\text{g}/\text{m}^3$ per day. It is interesting to

mention that the upper limits of SO₂ were exceeded at the beginning of June 2006 and June 2008.

In May 2006 the concentration of SO₂ was within the limited range (29 $\mu\text{g}/\text{m}^3$ per day) as in May 2008 (70 $\mu\text{g}/\text{m}^3$ per day). The upper limit of SO₂ was exceeded during one day in May 2008. The upper limit concentration of soot concentration was 50 $\mu\text{g}/\text{m}^3$ per day. The concentration of soot in June 2006 and in June 2008 varied within the limited range, and the upper limit was not exceeded.

DISCUSSION

The prevalence rate of symptomatic bronchial hyperresponsiveness in a random sample of 106 children in our region is 18% for crucial point of $PC20 = 4.1 \pm 3.03$ mg/ml and $PD20 = 3.22 \pm 2.59$ μmol methacholine. Chinn et al. [7] concluded that respiratory symptoms more frequently present in children from Australia, New Zealand, West Coast of America and England than in children from continental Europe. Peat et al. [8] from Australia found in his study that symptomatic bronchial hyperresponsiveness ranged from 19% in children that previously exhibited wheezing to 48% in children that exhibited wheezing during the last 12 months. Symptomatic bronchial hyperresponsiveness was reported by Ulrik [9] to be present in 15% of children from Denmark aged 7-17 years, by Siersted [10] in 75% of children aged 12-15 years, by Backer [11] in 35% and by Hansen et al. [12] in 82%. In Omaha, according to the results obtained by Hopp et al. [13], 98% of children express symptomatic bronchial hyperresponsiveness, whereas Popp et al. [14] reports 65% children who express symptomatic bronchial hyperresponsiveness in Austria. The prevalence rate of symptomatic bronchial hyperresponsiveness in our region is on average in relation to the prevalence rate in other countries worldwide.

During our research, we detected that asthmatic children expressed on average a moderate bronchial hyperresponsiveness which continued two years after prophylaxis by GINA and NAEPP.

Bronchial sensitivity in asthmatic children is approximately the same before and two years after administering the prophylaxis. However, bronchial reactivity is significantly lower two years after prophylaxis. In asthmatic children the change of FEV1 is significantly smaller, the velocity of change of slope dose response curve is faster, PCw is 2-3 times lower and bronchodilatation response ($+20\%$ FEV1) is slightly faster after two years of prophylaxis by GINA and NAEPP.

Children who exhibit moderate and severe bronchial hyperresponsiveness, low bronchial sensitivity to methacholine is followed by a prompt and elevated bronchial reactivity to methacholine, bearing in mind that after two years of conventional prophylaxis by GINA and NAEPP, the slope of dose response curve in the middle part has been milder. The smaller steep slope of the dose response curve shows that bronchoconstriction is milder after two years of prophylaxis. The airways of the treated and controlled asthmatic patient are less constricted; the growth of inflam-

mation cells is slower and they release constrictor mediators in small quantities, so that the child does not exhibit symptoms, or exhibits only mild symptoms of asthma after two years of conventional therapy [4, 5].

The children from our study had asthma exacerbations despite the fact that they needed prolonged treatment with the aim to reach minimal bronchial reactivity and high bronchial sensitivity.

After two years of conventional prophylaxis the children were free of symptoms and exhibited a moderate bronchial responsiveness. Devereux et al. [15], Avital et al. [16], Barr et al. [17] and Szefer et al. [18] explained that the reason for absent coordination between the patient's history and bronchoconstriction to methacholine is not due to poor perception, but to poor subjective description of the feeling of bronchoobstruction. Sunyer et al. [19] considered wheezing highly sensitive for bronchial hyperresponsiveness and that, in combination with bronchial hyperresponsiveness it was very specific for diagnosis of asthma.

Periodically high concentrations of SO₂ can have an important influence on the maintenance of the same degree of bronchial sensitivity despite treatment with anti-inflammatory medicines. After administering anti-inflammatory medicines, bronchial reactivity in every second asthmatic child (59%) is good. A fast change of bronchial reactivity in the remaining asthmatic children (41%) is contributed by aero-pollution with SO₂ and/or possibly insufficient and inadequate treatment effect. We conducted our research in urban environment, whereas according to the findings of Davies and Magnussen [20] the concentrations of SO₂ have been significantly increasing in rural areas during the last few decades as a result of boiler rooms, which is all reflected by increased morbidity of children suffering from respiratory and allergic diseases.

In May and June 2006 and 2008, we expected increased concentration of pollens in the air consisting mainly of grass pollen and of tree pollen, but we could not predict high concentrations of aero-pollutants. The data on exceeded allowable concentrations of SO₂ of over 150 µg/m³ per day, soot concentrations of over 50 µg/m³ per day and concentrations of total deposited substances of over 450 µg/m³ per day (minimally permitted concentration – MPC) was obtained after the completed research.

A grain of pollen attached to an aero-pollutant (ozone, SO₂, nitric dioxide – NO₂) has a greater influence on the increased release of histamine from the basophiles of a child with sensitivity to pollen [21]. In June both of 2006 and 2008, when we conducted the study on bronchial hyperresponsiveness in children, SO₂ exhibited a harmful effect on airway mucosa during a short period time. Neither the quantity of total deposited substances, nor the quantity of soot is a predictive factor of bronchial hyperresponsiveness. However, after a prolonged effect,

in conjunction with SO₂, it contributes to the change of bronchial responsiveness in children. Devalia et al. [22] consider that SO₂ provokes respiratory symptoms particularly dyspnoea, airway inflammation, and if combined with NO₂, it causes a strong bronchoconstriction in asthmatic children, decreases PD20 for 60.5%, causes dyspnoea and aggravates anaphylactic reaction. Bronchial hyperresponsiveness in asthmatic children to inhaled allergens is increased and maintained for 24 to 48 hours if the patient is exposed to inhalation of SO₂ in concentrations of 200 ppb (400 µg/m³).

A periodically high concentrations of SO₂ and a high quantity of total deposited substances over longer periods of time prior to this research, aggravated the antigen effect of pollen on airway mucosa. Moreover, they caused extensive inflammation, as well as airway reactivity, i.e. airway sensitivity mainly in children who had previously exhibited the symptoms of wheezing bronchitis, bronchial asthma, allergic rhinitis (hay fever) and/or atopic eczema. Taking into consideration that the school year ends in May and June, children spent more time at home (closed environment), so that the cumulative effect of pollen was only slightly detectable; contrarily, the onset of the cumulative effect of dust mite, house dust mite, house dust and other allergens in home environment could be clearly detected.

Bronchial reactivity in asthmatic children is multifactorially controlled. Immune, endocrine and nervous systems present a cohesive system of defence, and if the balance is disturbed in just one of them, a set of secondary exact consequences takes place in the remaining two systems. The consequences of the disturbed balance of the system in charge are corrected by anti-inflammatory and immunomodulatory therapy taken during the course of a couple of months, even years until the high bronchial sensitivity and low bronchial reactivity are reached. The bronchial responsiveness, mainly symptomatic, is increased both by biological risks, as well as by environmental risks, such as aero-pollution and pollen season.

Anti-inflammatory therapy by GINA and NAEPP is not as efficient as we expect. There is a possibility which could be taken into consideration that treatment with PRACTALL [23] could yield more desirable therapeutic effects.

CONCLUSION

According to our study, the optimal duration of anti-inflammatory treatment in asthmatic children who show moderate bronchial hyperresponsiveness should be longer than two years. Currently, we should take into consideration the possibility for a need of different consensus from the one we have been using.

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Промене преосетљивости бронхија код деце оболеле од бронхијалне астме

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КРАТАК САДРЖАЈ

Увод Преосетљивост бронхија је чинилац предвиђања бронхијалне астме независно од показатеља запаљења.

Циљ рада Циљ рада је био да се одреде учесталост и значајни фактори предвиђања преосетљивости бронхија, те установи дејство профилактичке терапије преписане према консензусима Глобалне иницијативе за астму (енгл. *Global Initiative for Asthma – GINA*) и америчког Националног програма за едукацију о астми и превенцији (енгл. *National Asthma Education and Prevention Program – NAEPP*) на преосетљивост бронхија код деце оболеле од бронхијалне астме.

Методе рада Преосетљивост бронхија је процењивана бронхопровокацијским тестом метахолином код 106 деце са бронхијалном астмом.

Резултати Преваленција преосетљивости бронхија праћене симптомима обољења била је 18% са просечном провоцирајућом концентрацијом PC_{20} од $4,1 \pm 3,03$ mg/ml и провоцирајућом дозом PD_{20} од $3,22 \pm 2,59$ μ mol метахолина. Деца оболела од астме показују углавном умерену преосетљивост, што се одржава и након две године профилактичке терапије. После овог периода лечења бронхијална реактивност је била слабија, промена FEV_1 значајно мања, брзина промене нагиба кривуље доза – одговор бржа, провоцирајућа кон-

центрација која узрокује шиштање у грудима (визинг) два-три пута мања, док је бронходилатацијски одговор био незнатно бржи. Благе кривуље доза – одговор указују на блажу бронхоконстрикцију после две године примене профилактичке терапије. Аерозагађење, односно неадекватно лечење били су разлог брже промене бронхијалне реактивности код 41% деце након две године. Истовремени и дуготрајни утицај алергена из кућне средине и повремено висока концентрација загађења ваздуха потенцијали су антигенско дејство полена трава и дрвећа на слузокожу дисајних путева, појачавали осетљивост бронхија, посебно код деце атопијске конституције, и интензивирали испољавање симптоматске преосетљивости бронхија. После две године примене профилактичке терапије, према консензусу *GINA* и *NAEPP*, деца нису имала симптоме астме или су се код њих испољавали благи симптоми обољења, али је осетљивост бронхија остала непромењена.

Закључак Оптимална дужина антиинфламаторне терапије бронхијалне астме код деце код које се испољава умерена преосетљивост бронхија треба да буде дужа од две године.

Кључне речи: преосетљивост бронхија; деца; бронхијална астма