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Influence of atopy and different treatments of asthma on fractional concentration of exhaled nitric oxide in children

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Exhaled nitric oxide fraction is a noninvasive surrogate measure of airway inflammation. Its levels are elevated in asthma patients. The interconnection between asthma inflammation and Exhaled nitric oxide fraction levels and how it is influenced by atopy and different therapeutic options have not yet been resolved. The study included 143 children, mean age 11.27 years, with asthma and positive allergy test results. Patients were treated for 6 weeks with montelukast or with a combination of inhaled corticosteroids and montelukast. Exhaled nitric oxide fraction was measured in all patients before (visit 1) and after treatment with montelukast or combined therapy (montelukast and inhaled corticosteroids) for 6 weeks (visit 2). Exhaled nitric oxide levels were significantly higher in children before than after treatment (mean 37.01±31.40, median 24.00 vs. 30.02±28.71 ppb, median 20.00; p<0.001). The children treated with montelukast for 6 weeks had statistically significant lower values of exhaled nitric oxide fraction. Accordingly, in children with allergic asthma, montelukast has a positive effect on airway inflammation as measured by the nitric oxide level.

Keywords: asthma; child; adolescent; montelukast; alergens; nitric oxide; pulmonary ventilation; respiration

INTRODUCTION

Pathophysiologically, asthma is a heterogeneous disease. Various phenotypes of asthma are characterized by different types of airway inflammation, different clinical course, and different response to therapy. Now, it is possible to assess airway inflammation in asthma patients by measuring the fractional concentration of exhaled nitric oxide (FeNO) during office visit. The National Asthma Education and Preventive Program (1) supports the use of FeNO in asthma patients, citing its reproducibility, association with markers of asthma severity, and its role in anti-inflammatory treatment. Several studies have shown elevated FeNO values in children with asthma or atopy (2-5). It has been shown that FeNO levels correlate with the degree of IgE sensitization, skin tests findings (6-8) and specific IgE antibody titers (9-11), and that it reflects subclinical bronchial inflammation in atopic subjects.

Short-term application of steroids can normalize eNO (12-14) and lead to significant improvement of lung-function variables in asthmatic children (15). The fact that eNO reflects local conditions in the airways makes it a suitable marker for monitoring an individual's response to inhaled corticosteroid (ICS) treatment (14, 16, 17), and to compare the efficacy of different ICS preparations (18). However, in some subjects with asthma, the eNO remains elevated in spite of treatment with high doses of ICS (19). In atopic subjects, this seems to be related to allergen exposure and degree of IgE sensitization. *Buchvald et al*. (20) have shown that asthmatic children in whom elevated NO levels persisted after high-dose ICS treatment had higher specific IgE titers than children whose NO levels were normalized. Leukotri-

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ene receptor antagonists (LTRAs) down-regulate eosinophilic inflammation by extranuclear mechanisms (21). LTRAs also reduce FeNO in patients with asthma (22-24).

The aim of this study was to evaluate the validity of FeNO in relation to atopy and lung-function parameters, before and after treatment with a variety of therapeutic options such as monotherapy with LTRAs and combined therapy with ICS in addition to LTRAs.

SUBJECTS AND METHODS

Study population

A total of 143 subjects (mean age 11.27±2.84; 86 male and 57 female) with asthma were recruited from outpatient divisions in two centers (Novi Sad and Niš) in Serbia. Asthma was diagnosed before treatment according to recommendations of the National Heart, Lung and Blood Institute (NHLBI) Expert Panel Report (1). Asthma was diagnosed based on clinical criteria, without confirmation of asthma by metacholine test. All subjects were between 7 and 18 years old, clinically stable, considered clinically well controlled and without symptoms of acute infection for more than one month before including in the study. There were no significant differences between the study groups according to age, sex and duration of illness. Also, there were no smokers. Exclusion criteria were: 1) history of viral infections in the last 4 weeks prior to inclusion in the study; 2) asthma attacks during the month preceding the start of the trial; and 3) chronic disease other than allergic disorders. Allergic sensitization was determined in all subjects by standardized skin prick tests (SPTs) to common aeroallergens grass pollen mix, tree pollen mix, wed pollen mix, dust mite mix, house dust mite (*Dermatophagoides pteronyssinus*), cat and dog epithelia, mold mix, and in addition, histamine and physiological saline acted as positive and negative control, respectively (Institute for Virusology, Vaccine and Serum, Torlak, Serbia). A wheal diameter of 3 mm or greater than the negative saline control was considered as positive result, and sensitization was confirmed. SPT response was converted into an atopic index (0: negative to all aeroallergens, 1: positive to 1-2 aeroallergens, 2: positive to 3-4 aeroallergens, 3: positive to more than 5 aeroallergens) to examine the effect of atopy on the FeNO level.

The study was approved by the institutional Review Board of the Institute for Child and Youth Health Care of Vojvodina in Novi Sad, and written consent was obtained for each child included in the study.

First group of patients (71 children) were those with intermittent asthma. Patients in this group were treated with LTRA (montelukast) for six weeks after the first visit. Second group of patients (72 children) included patients with mild persistent asthma, previously treated with low doses of ICS (less than 250 mcg of Beclomethasone or its equivalents). In these patients, montelukast was added to ICS on the first visit. FeNO levels were measured in all patients before (visit 1) and after the inception of treatment with montelukast or combined therapy (montelukast and inhaled corticosteroids) for a six-week period (visit 2).

FeNO levels were measured according to the ATS/ERS guidelines by using the NIOX NO monitoring system (Niox mino, Aerocrine AB, Solna, Sweden) (25) before spirometry tests, so all parameters were within the limits specified by the ATS guidelines. FeNO was measured online with an expiratory flow of 50 mL/s and subjects exhaled against resistance to prevent upper airway contamination.

Baseline spirometric parameters were recorded from the best of three attempts. In the Novi Sad center, a Master Screen IOS spirometer (Jaeger, Würzburg, Germany) was used, with measurements not varying by more than 5% or 0.2 liters according to ATS guidelines (26). Spirometry measurements in the Niš center were performed using a Spirovit SP1 spirometer (Schiller). The level of personnel education and training was recorded for both trial sites.

Data were analyzed using the statistical package for social sciences version 10.0 for Windows (SPSS, Inc., Chicago, IL, USA). Categorical variables were expressed as number of items and percentage. Continuous variables were expressed as mean ± standard deviation (and median). Data were tested for normality (Shapiro Wilk test). Comparison within groups was done using paired t test and Wilcoxon signed rank test. Comparison between two groups was done using the unpaired t test or Mann-Whitney U test. The Kruskal-Wallis test was used for comparison of 3 or more groups. Correlation between two variables was analyzed using Spearman's correlation coefficient. Univariate and multivariate regression analyses were performed to determine correlations between FeNo and other variables. A p value of <0.05 was considered statistically significant.

RESULTS

Patients included in the study were divided into two groups: group 1 included patients with intermittent asthma (n1=72; 50.34%) and group 2 patients with persistent asthma (n2=71; 49.66%). There were no significant between-group differences according to age, sex, duration of disease, atopic status and lung function at any time, except for FeNO before and after treatment.

The mean value of FeNO in the study group was 37.01±31.40 ppb at first visit and 30.02±28.71 ppb at second visit (after

treatment). Wilcoxon signed rank test confirmed the levels of FeNO to be significantly reduced after treatment.

The mean value of FeNO on the first visit (FeNO1) was 40.44 ppb in group 1 and 33.64 ppb in group 2. Mann-Whitney test showed that the mean values of FeNO1 were significantly lower in children with persistent asthma compared to FeNO in the group of children with intermittent asthma ($p<0.05$) at the time of first visit.

Our clinical trial confirmed that FeNO response was heterogeneous. The NIOX NO monitoring system detected a highly significant decrease in FeNO levels ($p<0.001$) after 6 weeks of treatment with LTRA in group 1 patients (Table 1).

Out of 143 children with asthma, 95 (66.43%) children had allergic rhinitis in addition to asthma. Statistical analysis (Table 2) showed that FeNO levels were significantly reduced in children with both diseases, asthma and allergic rhinitis ($p<0.01$) after 6 weeks of treatment, whereas in the group of patients without allergic rhinitis reduction did not reach the level of statistical significance ($p=0.0530$).

The mean values of FeNO during on the first and second examination were higher and in correlation with the increase of atopic index, although statistical significance was not proven (Kruskal-Wallis test). The mean values of FeNO in relation to atopic index are shown in Table 3. The mean values of FeNO after treatment were lower, but statistical significance determined by Wilcoxon signed rank test ($p<0.01$) was only found in patients with atopic index 2 (positive skin prick test to allergens 4). Near the level of statistical significance were cutback FeNO values in subjects with an AI 1 ($p=0.0633$).

The mean values FeNO1 and FeNO2 (at visit 1 and visit 2) were different, depending on the type of sensitization to inhaled allergens (Table 4): sensitization to seasonal allergens (27.13±21.80 and 19.33±9.33 ppb), perennial allergens (31.66±25.40 ppb and 28.46±28.01 ppb) and mixed type of sensitization (44.19±34.59 ppb and 36.26±32.51 ppb), respectively. Only patients with mixed type of sensitization had a statistically significant decrease ($p<0.01$) of FeNO levels after treatment. Non-atopic patients had the lowest values of FeNO (16.10±15.04 ppb) at visit 2.

The mean values of FeNO2 after treatment was significantly ($p<0.05$) lower in patients with sensitization to seasonal allergens compared with patients without sensitization to these allergens (Table 5). The mean values of FeNO were lower in both groups of patients after treatment, but in the group of patients with positive tests to seasonal allergens this decline was statistically significant ($p<0.01$).

The median value of FEV1 was 88.70% before treatment and 92.45% after treatment, which was a statistically significant improvement ($p<0.001$). Statistical analysis did not reveal correlation between baseline and post-treatment FeNO levels and FEV1 ($r=-0.05$; $p=0.267$ and $r=0.02$; $p=0.4025$, respectively).

TABLE 1. Influence of treatment on FeNO (ppb)

	Group 1 (n=71)	Group 2 (n=72)
NO1 (ppb)	40.44±29.01[a* b**] (33.00)	33.64±33.44 (21.00)
NO2 (ppb)	29.83±22.71 (23.00)	30.21±33.76 (17.00)
NO1-NO2 (ppb)	10.61±28.12 (5.00)	3.43±23.93 (1.50)
Relative change (%)	8.82±60.14 (19.00)	-8.50±68.95 (11.00)

[a] ICS *vs.* without ICS; [b] NO2 *vs.* NO1; *p<0.05; **p<0.001

TABLE 2. FeNO (ppb) and allergic rhinitis (AR)

Group	N (%)	FeNO1	FeNO2
Asthma + AR	95 (66.43%)	36.55±28.53 (26.00)	29.31±24.48[a**] (20.00)
Asthma	48 (33.57%)	37.94±36.72 (18.00)	31.44±35.91 (16.00)

[a] NO1 *vs.* NO2; **p<0.01

TABLE 3. FeNO (ppb) in relation to atopic index

AI	N (%)	NO1	NO2
Negative	10 (6.99%)	37.30±45.42 (15.50)	16.10±15.04 (10.00)
Positive to ≤2 allergens	77 (53.85%)	35.09±27.49 (23.00)	30.71±27.59 (20.00)
Positive to ≤4 allergens	41 (28.67%)	38.51±32.89 (28.00)	30.98±34.35** (20.00)
Positive to ≥5 allergens	15 (10.49%)	42.60±37.66 (26.00)	33.13±23.63 (20.00)

**p<0.01

TABLE 4. FeNO (ppb) and type of sensitization

SPTs	N (%)	NO1	NO2
Negative test	10 (6.99%)	37.30±45.42 (15.50)	16.10±15.04 (10.00)
Seasonal allergens +	15 (10.49%)	27.13±21.80 (20.00)	19.33±9.33 (19.00)
Perennial allergens +	56 (39.16%)	31.66±25.40 (21.50)	28.46±28.01 (18.50)
Mixed type sensitization	62 (43.36%)	44.19±34.59 (34.50)	36.26±32.51[b**] (24.00)

[b] NO2 *vs.* NO1; **p<0.01

TABLE 5. FeNO (ppb) before and after treatment and sensitization to seasonal allergens

	N (%)	NO1	NO2
Seasonal allergens +	77 (53.85%)	40.87±33.08 (30.00)	32.96±30.17[a*b**] (23.00)
Seasonal allergens -	66 (46.15%)	32.52±28.91 (19.00)	26.59±26.74 (16.00)

[a] positive *vs.* negative; [b] NO2 *vs.* NO1; *p<0.05; **p<0.01

There was positive correlation (Spearman's correlation coefficient) between duration of asthma and FeNO before (ρ=0.30; p<0.001) and after (ρ=0.23; p<0.01) treatment.

Univariate linear regression showed that the potential covariates that significantly affected FeNO1 levels were age, duration of illness (p<0.001) and mixed sensitization (p<0.05). The value of FeNO increased for 3.707 units (from 1.977 to 5.437) with each year of patient age and for 2.598 units (from 1.371 to 3.824) with each additional year of illness. The presence of mixed sensitization (external-seasonal allergen sensitization and home-perennial sensitization) increased FeNO for 12.675 units. Because of that, these parameters were included in multivariate regression model.

Multivariate linear regression analysis confirmed that statistically significant factors were patient age and duration of illness. The influence of mixed type of sensitization in this model was not proven. Each additional year of patient age increased FeNO1 levels for 2.337 (p<0.05) units, while prolonged duration of illness by each year increased FeNO1 levels for 1.503 (p<0.05) units. The model containing these three factors and the regression constant explains the variability of 16.1% in the sample FeNO1 values ($R^{2=0.161}$).

DISCUSSION

This study evaluated the impact of atopy and anti-inflammatory treatment on FeNO values in children with controlled asthma. Also, we analyzed the influence of comorbidities (allergic rhinitis) and lung function status on FeNO level.

A relationship between the fraction of exhaled nitric oxide (FeNO) and asthma was demonstrated in the 1990s with the finding of elevated FeNO in patients with asthma (27, 28). Many of the studies looking at the relationship between asthma and FeNO enrolled mainly atopic patients with asthma. Asthmatic children had significantly higher FeNO levels than non-atopic non-asthmatic controls (29). There has been much debate whether atopy is an independent factor for increased FeNO levels in non-asthmatic subjects. One large study in 157 children (30) showed that FeNO increased in relation to the number of positive skin prick reactions, but another study showed no difference in FeNO levels between atopic and non-atopic normal children (31).

In our study, children with intermittent and persistent asthma, as well as atopic and non-atopic, had increased values of FeNO in the stable phase of the disease. Elevated values of FeNO were strongly related to atopic index 2 (4 positive tests), which is consistent with the findings of other authors (32). Well-controlled atopic patients with asthma and patients with asthma and allergic rhinitis have similar values of FeNO. Some authors have shown variable nasal NO levels after exposure to allergens. Nasal NO, but not oral NO was significantly increased in subjects with seasonal allergic rhinitis during the pollen season (33). *Palm et al*. revealed no change in nasal NO levels in patients with allergic rhinitis, whereas in that study orally exhaled NO was increased (34). Other authors also failed to find an evident increase in nasal NO in seasonal rhinitis out of the pollen season (35) and during the pollen season (36). Our study showed that FeNO levels were similar in children with "pure" asthma and children with asthma associated with allergic rhinitis, although the study was conducted during pollen season (between June and October), i.e. when inhalant allergens like grass and weed pollens are dominant. Similar findings are reported by other authors (35, 36).

Corticosteroids are the most effective therapy for asthma, and current guidelines emphasize their use in all but mild asthma (1). Corticosteroid therapy down-regulates airway inflammation and improves lung function (35, 36). Airway inflammation in asthma is characterized by infiltrates of several cell types, including T-lymphocytes, macrophages, and eosinophils. Although many cell types have been shown to play an important role in disease activity, asthma may occur in the absence of one or more of those "effector" cells. Exhaled NO, a marker of airway inflammation, is increased in asthma and is extremely sensitive to steroid treatment. It can be used as a noninvasive standardized method of asthma monitoring. A significant reduction in exhaled NO has been reported after 6 hours following a single high dose of nebulized budesonide in symptomatic moderate asthma (37) or within 2-3 days after high-dose inhaled corticosteroids (38). A gradual reduction in exhaled NO is seen during the first week of regular treatment, with maximal effect between 3 and 4 weeks (37). Exhaled NO was able to differentiate between children shortly treated with or without steroids, the conventional lung-function variables, however, could not. In practice, exhaled NO may thus be a valuable parameter to monitor adherence to steroids, but less suitable to describe physiologically relevant impairments of lung function (39). Kharitonov et al. report that measurement of exhaled NO levels can indicate a dose-dependent onset and cessation of anti-inflammatory action of inhaled corticosteroids in patients with mild asthma (14).

In our study, patients that were treated with low doses of ICS achieved full and complete control of symptoms, but nevertheless, they had elevated levels of FeNO. Their clinical condition was stable, so the treatment was continued with the same (low) doses of ICS, but with the addition of LTRA (montelukast). The NIOX NO monitoring system detected a highly significant decrease in FeNO levels (p<0.001) after 6 weeks of treatment with LTRA (Table 1), which is in keeping with the results of many previous reports (40). The possible

explanation for the significant decline of FeNO levels in the group of children treated with LTRA is that this category of patients had intermittent asthma, or that airway inflammation is mediated by other mechanisms, so montelukast alone is sufficient for the control of the disease.

The authors are aware of some limitations of the study. This was an open-label, non-controlled study. In our study design, montelukast was added to inhaled corticosteroids; so, we cannot exclude the possibility that further improvements were the result of a longer period of treatment with inhaled corticosteroid rather than the addition of a second medication. Also, some of the nonsignificant trends we observed (for example, the group of asthma without rhinitis) could have proved to be significant in a larger sample population.

In conclusion, our study demonstrated that montelukast decreased the levels of FeNO in children with allergic asthma and, hence, that anti-inflammatory treatment with montelukast over a short period can be beneficial. We concluded that montelukast may be a good alternative for first-line anti-inflammatory treatment in children with allergic asthma in general, and in particular, in children who display the lack of cooperation with inhaled therapy.

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DOPRINOSI AUTORA/*DECLARATION OF AUTHORSHIP*

Svi autori su jednako doprinijeli u radu: sudjelovali u izradi rukopisa, prikupljanju, obradi, analizi i tumačenju podataka, prikupljanju literature i pisanju/*All authors contributed equally to this paper: participated in drafting the manuscript, collection, processing, analysis and interpretation of data, the collection of literature and writing*

SUKOB INTERESA/*CONFLICT OF INTEREST*

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SAŽETAK

Utjecaj atopije i različitih tretmana astme na koncentraciju izdahnutog dušičnog oksida kod djece

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Određivanje frakcije izdahnutog dušikova monoksida neinvazivna je metoda za dijagnozu upale dišnih putova. Njegova razina povišena je u bolesnika s astmom. Povezanost između astme i razine frakcije izdahnutog dušikova monoksida, kao i kako na tu povezanost utječe atopija i različiti terapijski pristupi astmi, još i sad nisu dovoljno razjašnjeni. Istraživanje je obuhvatilo 143-je djece prosječne dobi 11,27 godina s astmom i alergijom. Bolesnici su liječeni 6 tjedana montelukastom ili kombinacijom inhalacijskih kortikosteroida i montelukasta. Razina frakcije izdahnutog dušikova monoksida mjerena je u svih bolesnika prije (posjet 1) i nakon 6 tjedana liječenja montelukastom ili kombiniranom terapijom (posjet 2). Koncentracija izdahnutog dušikova monoksida bila je značajno viša u djece prije, negoli nakon tretmana (37,01±31,40 ppm, medijan 24,00 vs 30,02±28,71 ppm medijan 20,00, p<0,001). Djeca koja su liječena montelukastom 6 tjedana imala su statistički značajno niže vrijednosti frakcije izdahnutog dušikova monoksida. U djece s alergijskom astmom montelukast ima pozitivan učinak na upalu dišnih putova.

Ključne riječi: astma; djeca; adolescent; montelukast; alergeni; dušikov monoksid; plućna ventilacija; respiracija