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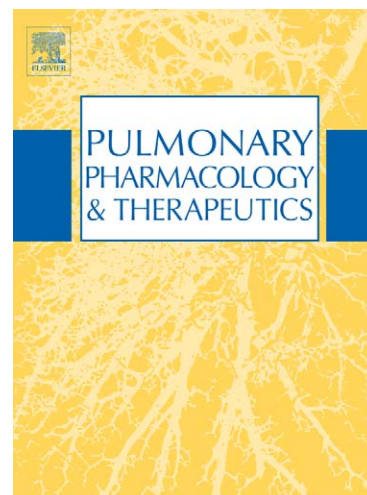
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**A randomized, double-blind trial of the effect of anti-asthma treatment on lung function
in children with asthma**

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Abstract

Background: Pulmonary function tests (PFTs) and especially spirometry measures are useful tools in evaluating early response to treatment of asthma in children mainly due to their worldwide availability. The aim of our study was to determine the effects of anti-asthma treatment in children, equally on FEV₁, FEF_{25-75%}, Rint and SRaw values.

Methods: Children 6-18 years of age with moderate atopic asthma were randomized to 4-week, placebo-controlled, double-blind trial. Patients were randomly allocated to receive 200 µg budesonide (B) (n=29), 5 or 10 mg (according to age) montelukast (M) (n = 29), 200 µg B + 5 or 10 mg M (n = 29), 200 µg B + 9 µg formoterol (F) (n=29) or placebo (n = 27). FEV₁, FEF_{25-75%}, Rint, SRaw were measured before and after treatment.

Results: Rint, SRaw, FEV₁ improved significantly in all active treatment groups while FEF_{25-75%} improved significantly only in BM group and M group. Combination therapy, showed significantly greater effects on Rint than monotherapy: BM group compared to B group ($P = 0.01$) and M group ($P = 0.03$) and BF group compared to B group ($P = 0.01$) and M group ($P = 0.04$).

Conclusion: This study shows that using single parameter for monitoring asthma can be misleading. Using combination of lung function techniques provides better assessment of treatment. Results of our study confirm this hypothesis. The best effect on large and small airways was achieved with combined anti-inflammatory therapy.

1. Introduction

Asthma is one of the most common chronic disease worldwide, imposing a substantial social burden on both children and adults [1]. Normal lung function is one of the goals of asthma management [1].

Symptom scores (SSc) and pulmonary function tests (PFTs) determine asthma severity and medication requirements [1]. Exacerbation rates, frequency of daytime and nocturnal symptoms, and caregiver assessments of quality of life can be useful measures in evaluating outcomes in children with asthma [2,3]. PFTs and especially spirometry measures are useful tools in evaluating early response to treatment of asthma in children mainly due to their worldwide availability. What needs to be kept in mind, especially in assessing early treatment effect of allergic inflammation in children with asthma, is that SSc and spirometry measures have also limitations, mainly their subjectivity (SSc), wide variability, and lack of stability in short time period (SSc and FEV₁). Spirometry measures possess other disadvantages, like the influence of forced maneuvers on airway tone, requiring child cooperation and, even in symptomatic children, being often within the normal range [4].

Additional PFTs such as resistance by the interrupter technique (Rint), plethysmography seem to be helpful additional tools evaluating early treatment effect of allergic inflammation in children with asthma. They assess airway resistances during quiet breathing, do not require active cooperation from children. It was shown that specific airway resistance (SRaw), Rint but not forced expiratory volume in one second (FEV₁) detected the subclinical increase in bronchial muscle tone in children [5]. It was revealed that, even in healthy children, salbutamol inhalation reduces the value of SRaw suggesting that plethysmography [6] can detect minimal changes in airway caliber [7]. From the studies reported to date some authors

[8,9] have confidence that Rint and SRaw are clinically useful, may precisely follow changes in lung function with growth and development and be used to manage lung disease in children, despite some reservations like questioning its repeatability. The interrupter technique has been shown to have a good short term repeatability (over a time span of minutes) in children [8]. Greater long term variability between measurements was found in children with persistent cough or previous wheeze [8], which suggests that the lower long term repeatability in symptomatic children might be due to the variability of the disease rather than the variability of the technique. On the other hand poor stability and wide variability of FEV₁ in many studies was observed [10,11], suggesting the need of additional lung function tests usage that could accompany spirometry in studies of treatment monitoring in children with asthma.

Regular anti-asthma treatment with inhaled glucocorticosteroids improves lung function [12], prevents bronchoconstriction, decreases symptoms, reduces asthma exacerbation [13]. There is evidence that leukotriene modifiers used as add-on therapy reduce the dose of inhaled glucocorticosteroids in moderate to severe asthma, and may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids alone [14-17]. Some authors demonstrate equivalent effects of long-acting inhaled β 2-agonists and leukotriene modifiers as add-on therapy on asthma exacerbations [13]. However, recent findings of Bisgaard [18] and Ni [19] showed the lack of evidence for the control of asthma exacerbations in children regularly using long-acting inhaled β 2-agonists and one of these studies [18] has brought into question its general use as add-on therapy in children.

Different surveys also revealed insufficient monitoring of asthma and its treatment [20-22]. Previous research indicates that lung function testing can provide a substantial insight into the outcome of asthma. However focusing on single parameter i.e. FEV₁ may underestimate bronchial obstruction [22], mainly because it reflects large and medium-size airway function

[23]. Even though there is no direct parameter capable of assessing small airways, it has been assumed that the forced expiratory flow at the 25 and 75% of the pulmonary volume (FEF₂₅₋₇₅) might be considered as a measure of the caliber concerning distal airways [24, 25, 26], where airflow limitation is mainly dependent on asthmatic inflammatory process intensity, not due to bronchial muscle constriction. Rint has been shown to measure fall in resistive pressure across the airways [8]. SRaw is the pletysmographic parameter which also measures total airway resistance ($sRaw = \text{Thoracic gas volume} \times \text{Absolute airway resistance}$) [27, 28]. That is why Rint and SRaw measures are thought to precisely assess resistances across all the airways, where airflow limitation is dependent on all pathological features of asthma, including bronchial smooth muscle constriction and hypertrophy [1, 8, 28]. Thus, measurement of all above parameters together, may reflect airway changes in asthmatic children in the best way and optimally assess the effect of treatment.

The aim of this study was to determine the effects of anti-asthma treatment on measurement of FEV₁, FEF_{25-75%}, Rint and SRaw values in children with moderate atopic asthma.

2. Patients and methods

2.1. Patients

Participants in the 8-week study comprised of 150 children with a typical history of moderate asthma who were sensitive to house dust mites as shown by positive skin-prick tests and by the presence of specific IgE to *Dermatophagoides pteronyssimus* or *Dermatophagoides farinae* (41 patients positive to *Dermatophagoides pteronyssimus*, 54 patients positive to *Dermatophagoides farinae* and 55 patients positive to both *D. pteronyssimus* and *D. farinae*). Diagnosis of asthma was established by symptoms of asthma and improvement in the prebronchodilator FEV₁ of $\geq 15\%$ after administration of salbutamol (200 μ g). We defined moderate persistent asthma according to established guidelines [1]. During the previous 6 months, before the study, all patients had been treated with inhaled steroids (budesonide,

average dose 400 µg /day) and with long-acting bronchodilator (formoterol, 0.012 mg twice daily). Antihistamines (loratadine, 10 mg daily), nasal steroids (budesonide, 0.05 mg daily), and nasal nedocromil (nedocromil sodium, 2.6 mg four times daily) were also used. Asthma was stable in all patients, there had been no exacerbations of disease or need for other treatment for 6 months, and no hospitalisations due to asthma occurred in the previous 6 months before the study.

For the purposes of the study skin prick tests (Nexter-Allergopharma, Germany) to standard allergen extracts were performed; a mean wheal diameter ≥ 3 mm at 15 min was defined as a positive response. Serum-specific IgE levels were measured by using a Pharmacia CAP kit (Uppsala, Sweden); >0.7 kU/L were defined as positive. Subjects were recruited from our Clinic Center.

Inclusion Criteria

Male and female outpatients, aged 6 to 18 with a clinical diagnosis of bronchial asthma with a duration of at least 6 months before the first visit and with current history of moderate persistent asthma, were enrolled. To become eligible for the active treatment period, patients and their parents were required to do reproducible spirometry, whole body pletysmography and interrupter technique.

Exclusion Criteria

Study exclusions included active upper respiratory tract infection within 3 weeks before the study and acute sinus disease requiring antibiotic treatment within 1 month before the study, previous intubation, or asthma hospitalisation during the 3 months before the first visit. Additional criteria were other clinically significant pulmonary, hematologic, hepatic, gastrointestinal, renal, endocrine, neurologic, cardiovascular, and/or psychiatric diseases or malignancy that either put the patient at risk when participating in the study or could influence the results of the study or the patient's ability to participate in the study as judged by the

investigator. Excluded medications were β -blockers (eye drops included), astemizole within 3 months, or oral corticosteroids within 1 month before the first visit. Patients who were receiving immunotherapy were also excluded.

2.2. Study Design

A schema showing the flow of subjects through the trial is shown in Figure 1. The study was conducted from April to October, when the exposure to dust mites was at the constant level. This was a randomized, double-blinded, placebo-controlled trial comparing the effect of budesonide, montelukast, budesonide with montelukast, budesonide with formoterol and matching placebo. We measured PFTs such as FEF_{25-75%}, Rint, SRaw and FEV₁ before and after treatment. Children 6-14 years received 5 mg of montelukast (Singulair, MSD, Whitehouse Station, NJ, USA) and children > 14 years old received 10mg oral tablet once daily at bedtime. Budesonide (Pulmicort turbuhaler, AstraZeneca, UK) was administered 200 μ g per day, formoterol (Oxis turbuhaler, AstraZeneca, UK) was administered 9 μ g per day. Montelukast, placebo, turbuhalers containing drug or no drug were blinded by the hospital pharmacy.

There were three study visits. At the first visit, long acting β ₂-agonists, steroids, nasal cromolyn, and antihistamines were stopped, and patients were put on inhaled β ₂-agonist, (Ventolin, GlaxoSmithKline, USA) 100 μ g/dose 'as needed' for symptomatic relief purposes. They were informed of the aim of the study and were told how to use the inhalers. At the second visit, 4 weeks after the first visit, patients were randomized according to a computer-generated allocation schedule for anti-asthma treatment with:

- budesonide, montelukast placebo, formoterol placebo (29 patients) - budesonide group
- montelukast, formoterol placebo, budesonide placebo (29 patients) - montelukast group
- budesonide, montelukast, formoterol placebo (29 patients) – budesonide with montelukast

group

- budesonide, formoterol, montelukast placebo (29 patients) –budesonide with formoterol

group

- montelukast placebo, formoterol placebo, budesonide placebo (27 patients) – placebo

group

At visit two and three spirometry, whole body plethysmography and interrupter technique were performed. This always took place at the same time of day (11 a. m.) and on the same day of the week. Before lung function testing all drugs were withheld for 24 hours. The measurements of FEF_{25-75%}, FEV₁, Rint and SRaw, were recorded at visit two and three.

2.3. Lung function measurements

Pulmonary function testing was done with a LUNGTEST 1000 unit (MES, Cracov, Poland). Flow and volume were measured with a pressure-screen-type pneumotachograph, calibrated daily. All measurements were performed by trained investigators. The sequence of measurements was Rint, whole body plethysmography and spirometry. Measurements were carried out in a familiar and quiet room. Standing height and weight were assessed: subjects were measured without shoes, wearing light summer clothing. During measurements, children were instructed to sit upright, and a nose clip and a noncompressible mouthpiece were used. When needed, an adult accompanied the subject during testing. Predicted values for all lung function variables were based on a previous study of healthy controls, provided by the lung function test equipment manufacturer [29, 30]. Mean relative change normalizes lung function improvement over a wide of baseline lung function and was defined as:

$$\frac{\text{PFT at the end of the study} - \text{PFT at the start}}{\text{PFT at the start}} \times 100\%$$

PFT: pulmonary function test

FEV₁ and FEF25-75%

A spirometer was used to measure FEV₁ and FEF25-75%. The tests were performed according to American Thoracic Society standards [31]. The highest of three successful measurements was taken. The results were expressed as percentage of change from baseline.

SRaw

Measurements were made during tidal breathing. SRaw was measured in a constant-pressure, whole-body plethysmograph as the relationship between simultaneous variations in respiratory flow and maximum changes in plethysmographic pressure during inspiration and expiration. SRaw was calculated from the S-shaped resistance loops presented graphically by the computer connected with the plethysmograph. The relationship between flow and pressure was displayed on-line. The measurement was rejected if any alteration in the shape of the resistance loops was seen, since this could reflect face mask leakage, coughing, swallowing, or vocalization. Compensation for body temperature, barometric pressure, and water vapor-saturated (BTPS) conditions was done electronically [32]. The respiratory rate was 30 to 45 breaths/min. The mean value of three sequential measurements of SRaw was used as the result. The results were expressed as percentage of change from baseline.

Rint

Measurements were carried out using the LUNGTEST 1000 Unit, device including a shutter and pneumotachograph, connected to computer with an online display showing mouth pressure, time of shutter closure and Rint values recorded during one session. Its software calculates Rint using the back extrapolation technique to $t = 15$ ms after shutter closure during 100 ms. Measurements were made during tidal breathing. The position of the pneumotachograph with Rint was adjusted on a support arm to facilitate unobstructed breathing. The functioning of the shutter was demonstrated once to make children familiar

with the sound. A number of 5 correct tracings was then obtained for the expiratory maneuver. During this period the cheeks and chin were supported from behind by the observer, the head was positioned in slight extension. Shutter closure was programmed at maximal expiratory tidal flow. Thus, R_{int} values are obtained at or near midexpiration, minimizing the breath-to-breath variation in inflation level and hence on R_{aw} . Timing of the shutter closure (at the peak of flow) can be checked on the display. Tracings were inspected immediately after the measurement in the presence of the child. Rejection criteria were: tachypnea, usage of the vocal cords, extreme neck flexion or extension, leakage of the mouthpiece. Tracings not showing the timing of the shutter closure were discarded; tracings with a horizontal or declining pressure signal after shutter closure were considered artifacts owing to air leakage or altered ventilation pattern and were discarded as well [33]. The mean value of five consecutive measurements was used as the result. The results were expressed as percentage of change from baseline.

2.5. Statistical methods.

The results were analyzed according to well known statistical methods by using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc., Tulsa, USA). Data was presented as mean with standard error (SEM) or standard deviation (SD) (for demographic data). Before analysis all parameters were logarithmically transformed to the normal distribution. To determine differences within groups Student's t-test was used. To compare changes with treatment between groups all parameters were analyzed using analysis of variance (ANOVA) for repeated measures. P-values < 0.05 were considered to be significant.

2.6. Ethics

This study was approved by the Medical Ethics Committee of the Medical University. All parents or guardians gave their written consent for participation in this study. The families

were fully informed that treatment withdrawal during wash-out period might result in a significant exacerbation of asthma and they were given a specific plan to manage any exacerbation that might occur.

3. Results

One hundred and forty three subjects completed the study, 29 from montelukast group, 29 from budesonide group, 29 from montelukast with budesonide group, 29 from formoterol with budesonide group, 27 from the placebo group. Seven patients were withdrawn from the study because of asthma exacerbation due to respiratory tract infection (5 patients during the first 4 weeks of treatment with Ventolin alone, and 2 patients from placebo group, during active treatment period). There were no meaningful differences between the treatment groups in demographic parameters or baseline characteristics. Characteristic of the patients who completed the study is presented in Table 1.

Mean baseline lung function measured as SRaw and Rint at the day of randomization was 170.3% (95% CI: 163.4 to 177.2), and 128.2% (95%CI: 123.2 to 133.1) respectively, of the predicted lung function values (i. e. the subjects showed significantly increased airway resistance at baseline).

Lung function was significantly improved after 4 weeks of treatment with budesonide, montelukast, budesonide with montelukast, and budesonide with formoterol and it was reflected by Rint, SRaw and FEV₁ within groups and compared to placebo at the endpoint after 4 weeks of treatment (Table 2).

Rint, SRaw and FEV₁ improved during active treatment period and deteriorated during administration of placebo (Table 2, Figure 2).

Additionally it was found that FEF_{25-75%} values improved significantly after 4 weeks of

treatment with montelukast and budesonide with montelukast within groups and compared to placebo (Table 2, Figure 3).

Analysis of variance (ANOVA) showed no significant differences between active treatment groups in changes of SRaw and FEV₁. However, we found significant difference between active treatment groups in Rint (Figure 2). Rint improved more significantly in budesonide with montelukast group compared to budesonide group ($P=0.01$) and compared to montelukast group ($P=0.03$). Also in budesonide with formoterol group compared to budesonide group ($P=0.01$) and compared to montelukast group ($P=0.04$), Rint improved more significantly.

4. Discussion

This is the first trial using measurement of FEV₁, FEF_{25-75%}, Rint and SRaw after the different therapeutic combinations for the management of childhood asthma. There have been many studies on this topic, however, none of them used the combination of various techniques to differentiate central and peripheral airway obstruction. In previous studies, rather single drug treatment effect on lung resistance parameters was assessed [34-38].

Our study showed that budesonide, montelukast, budesonide with montelukast, and budesonide with formoterol significantly improved lung function based on FEV₁, Rint and SRaw values after four weeks of treatment. We also showed that monotherapy with montelukast and montelukast combined with budesonide increased FEF_{25-75%} confirming that montelukast improved the airflow in small airways in our patients. According to the Rint results, we demonstrated that combination therapy showed significantly greater effects than monotherapy across the airways (on large and small airways).

Although prior to the study all patients had been treated with budesonide and formoterol in doses higher than that of the study period, because of the fact that asthma was stable at least

from six months, we were able to modify treatment.

The present study was explorative and the low dose of budesonide was chosen with a view towards not overlooking any possible effect of other studied drugs on lung function. This low dose of budesonide was chosen to compare it favourably with the effects of montelukast. The justification for using montelukast alone for the therapy of moderate persistent asthma is to assess the single effect of montelukast on lung function in children.

There are many data showing significant improvement in lung function (based on FEV₁ or/and PEF results) in children with asthma treated with anti-leukotrienes [39, 40] inhaled steroids [39,41], anti-leukotrienes with inhaled steroids [42], long acting β 2-mimetics with inhaled steroids [43]. Nevertheless, there is limited data showing an efficacy of treatment based on FEF25-75%, SRaw and Rint measurements in children with asthma.

While currently glucocorticosteroids remains the reference drug as a controller in moderate persistent asthma, the study data demonstrated that administration of montelukast provided an important and additional effect on peripheral airways function in children. Moderate improvements in lung function, by means of spirometric measurements (in children 6 and older) and in asthma control (in children 2 and older) have been demonstrated with leukotriene receptor antagonist monotherapy in patients with severe and moderate disease [40, 44, 45]. In his latest cross-over study Szeffler et al. showed that phenotype of children with mild-to-moderate asthma, with normal pulmonary function and low levels of markers associated with allergic inflammation could receive montelukast as initial therapy with an assessment in response [39]. However, some severe asthmatics could be particularly sensitive to the positive effects of montelukast [46].

In our study we revealed that children treated with montelukast, either in monotherapy or in

combined therapy with budesonide demonstrate increase in FEF25-75% values after four weeks of treatment. This suggests that systemic drugs – like oral montelukast – can reach lower airways, whose inflammation plays a crucial role in the evolution of asthma, while inhaled drugs hardly reach them. Study of Nieto et al. showed good effect of montelukast on small airways measured by impulse oscillometry in children but there was no effect on FEF25-75% parameter [47]. Only one study in adults with moderate persistent asthma revealed that montelukast in combination with salmeterol improved FEF25-75% after 2 weeks of treatment [48]. Results of the two studies in children with asthma revealed that also budesonide monotherapy significantly improves FEF25-75% values [49, 50].

SRaw and Rint values were used to assess efficacy of treatment with budesonide [51], montelukast [34, 52], formoterol [35, 36], salmeterol [53], and fluticasone [37] in children with asthma. Study of Tomac et al. showed high efficacy of salmeterol administered for four weeks together with corticosteroid and disodium cromoglycate maintenance treatment by improving airway resistance and conductance [52]. In our study we also revealed significant decrease of SRaw together with Rint values within group of children treated with budesonide with formoterol. The effect of treatment on SRaw with one dose of formoterol was investigated and compared with one dose of salbutamol by Von Berg et al [35]. In this study formoterol produced a larger decrease in SRaw from baseline for longer periods after inhalation than did salbutamol, what was observed also in other study [38].

Study of Nielsen and Bisgaard revealed that Rint but not SRaw improved during treatment with budesonide in preschool children with asthma [51]. Also results of study of Pao and McKenzie outline the improvement in Rint after treatment with fluticasone in younger wheezy children sensitized to common aeroallergens [37]. In our study we observed significant improvement of Rint and SRaw after treatment with 200 µg of budesonide.

However we demonstrated that addition of montelukast or formoterol to budesonide therapy was associated with significantly greater improvements in Rint. Rint perform better than SRaw in terms of discriminating responses in the groups that received some form of chronic anti-inflammatory therapy. The basic assumption underlying the interrupter technique is that, following an instantaneous interruption of airflow at the airway opening (by closing a valve or shutter), there is an instantaneous equilibration of pressure between the alveoli and the airway opening (behind the occlusion) [8]. Rint has been shown to measure fall in resistive pressure across the airways, and includes also all Newtonian resistance from the respiratory system including components from the pulmonary tissues and chest wall [8], while SRaw concentrates specifically on airway resistance measurement [28]. We can speculate that the difference between the spectrum of these two measurements was responsible for greater significant improvement in Rint value in comparison with SRaw value after both combined therapies in our study.

In our study the lung function parameters in the active treatment groups improved compared to a deterioration in the placebo group. This certainly underscores the importance of objective monitoring of lung function in children with asthma. All patients from our study groups were able to easily perform all manouvers required for PFTs studied.

The aim of our study was to determine effect of anti-asthma treatment in children, equally on FEV₁, FEF_{25-75%}, Rint and SRaw values. There is no one single lung function parameter nor comparison as primary outcome in this study; there are four different treatment groups. In this case it did not allow us to adequately estimate power and sample size for our study.

This study shows that using single parameter for monitoring asthma can be misleading. Using combination of lung function techniques provides better assessment of treatment. Results of our study confirm this hypothesis. The best effect on large and small airways was achieved

with combined anti-inflammatory therapy. Our results are enhancing, and demand verification in the future.

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There is no conflict of interest.

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References

1. NIH Publication. Global Strategy for Asthma Management and Prevention. No 02-3659
Issued January, 1995. Updated 2004 from the 2003 document.
2. Skoner D P. Outcome Measures in Childhood Asthma. *Pediatrics* 2002;109:393-8.
3. Sharek PJ, Mayer ML, Loewy L, Robinson TN, Shames RS, Umetsu DT, Bergman DA.
Agreement among measures of asthma status: a prospective study of low-income children
with moderate to severe asthma. *Pediatrics* 2002 ;110:797-804.
4. Black J., Baxter-Jones AD, Gordon J, Findlay AL, Helms PJ. Assessment of airway
function in young children with asthma: comparison of spirometry, interrupter technique,
and tidal flow by inductance plethsmography. *Pediatr Pulmonol* 2004;37:548-53.
5. Davis SD. Neonatal and pediatric respiratory diagnostics. *Respir Care* 2003;48:367-85.
6. Hellinckx J, De Boeck K, Bande-Knops J, van der Poel M, Demedts M. Bronchodilator
response in 3-6,5 yeras old healthy and stable asthmatic children. *Eur Respir J*
1998;12:438-43.
7. Malmberg LP, Pelkonen A, Poussa T, Pohianpalo A, Haahtela T, Turpeinen M.
Determinants of respiratory system input impedance and bronchodilator response in
healthy Finnish preschool children. *Clin Physiol Funct Imaging*. 2002;22:64-71.
8. Sly PD, Lombardi E. Measurement of lung function in preschool children using the
interrupter technique. *Thorax* 2003;58:742-4.
9. Bisgaard H, Klug B. Lung function measurement in awake young children. *Eur Respir J*
1995;8:2067-75.
10. Nakaie CM, Rozov T, Manissadjian A. A comparative study of clinical score and lung
function tests in the classification of asthma by severity of disease. *Rev Hosp Clin Fac*

Med Sao Paulo. 1998;53:68-74.

11. Studnicka M, Frischer T, Neumann M. Determinants of reproducibility of lung function tests in children aged 7 to 10 years. *Pediatr Pulmonol* 1998;25:238-43.
12. Bousquet J, Aubier M, Sastre J, Izquierdo JL, Adler LM, Hofbauer P Rost KD, Harnest U, Kroemer B, Albrecht A, Bredenbroker D. Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma. *Allergy* 2006;61:72-8.
13. Bjermer L, Bisgaard H, Bousquet HJ, Fabbri LM, Greening AP, Haahtela T, Holgate ST, Picado C, Menten J, Dass SB, Leff JA, Polos PG. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomized, comparative trial. *BMJ* 2003;327:891-6.
14. Riccioni G, Della Veccia R, D'Orazio N, Sensi S, Guagnano M.T. Comparison of montelukast and budesonide on bronchial reactivity in subjects with mild-moderate persistent asthma. *Pulm Pharmacol Ther* 2003;16: 111-4.
15. Christian Virchow J, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med* 2000;162:578-85.
16. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, Konstantopoulos S, Rojas R, van Noord JA, Pons M, Gilles L, Leff JA; Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58:211-6.

17. Vaquerizo MJ, Casan P, Castillo J, Perpina M, Sanchis J, Sobradillo V, Valencia A, Vereá H, Viejo JL, Villasante C, Gonzalez-Esteban J, Picado C; CASIOPEA (Capacidad de Singulair Oral en la Prevención de Exacerbaciones Asmáticas) Study Group. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;58:204-10.
18. Bisgaard H. Effect of long-acting beta2 agonists on exacerbation rates of asthma in children. *Pediatr Pulmonol* 2003;36:391-8.
19. Ni CM, Greenstone I, Ducharme F. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. *Cochrane Database Syst Rev* 2005;18:CD005307.
20. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802-7.
21. van den Berg NJ, of ten Have WH, Nagelkerke AF, Bindels PJ, van der Palen J, van Aalderen WM. What general practitioners and paediatricians think about their patients' asthma. *Patient Educ Couns.* 2005;59:182-5.
22. Hanania NA. Revisiting asthma control: How should it best be defined? *Pulm Pharmacol Ther.* 2006; in press.
23. Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000;105:354-8.
24. Bjermer L. Past and future perspectives in the asthma treatment. *Resp Med* 2001 ;95:703-19.
25. Ferguson AC. Persisting airway obstruction in asymptomatic children with asthma with normal peak expiratory flow rates. *J Allergy Clin Immunol* 1988;82:19-22.

26. Bye MR, Kerstein D, Barsh E. The importance of spirometry in the assessment of childhood asthma. *Am J Dis Child* 1992;146:977-8
27. Olaguibel JM, Alvarez-Puebla MJ, Anda M, Gomez B, Garcia BE, Tabar AI, Arroabarren E. Comparative analysis of the bronchodilator response measured by impulse oscillometry (IOS), spirometry and body plethysmography in asthmatic children. *J Investig Allergol Clin Immunol* 2005;15:102-6.
28. Larsen G, June-Ku BK, Guilbert T, Morgan W. Assessing respiratory function in young children: Developmental considerations. *J Allergy Clin Immunol* 2005;115:657-66.
29. Quanjer PhH ed. Standardisation of lung function tests. 1993 Update. Report Working Party for the European Community for Steel and Coal. *Eur Respir J* 1993;6:Suppl. 16
30. Quanjer PhH, Helms P, Bjure J, Gaultier CI. Standardisation of lung function tests in pediatrics. *Eur Respir J* 1989;2:Suppl.4
31. Crapo RO, Hankinson JL, Irvin C. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107-36.
32. Klug B, Bisgaard H. Measurement of the specific airway resistance by plethysmography in young children accompanied by an adult. *Eur Respir J* 1996;10:1599-605.
33. Merkus PJ, Mijnsbergen JY, Hop WC, de Jongste JC. Interrupter resistance in preschool children: measurement characteristics and reference values. *Am J Respir Crit Care Med* 2001; 163:1350-5.
34. Bisgaard H, Nielsen KG. Bronchoprotection with a leukotriene receptor antagonist in asthmatic preschool children. *Am J Respir Crit Care Med* 2000;162:187-90.

35. von Berg A, Berdel D. Formoterol and salbutamol metered aerosols: comparison of a new and an established beta-2-agonist for their bronchodilating efficacy in the treatment of childhood bronchial asthma. *Pediatr Pulmonol* 1989;7:89-93.
36. Kozlik-Feldmann R, von Berg A, Berdel D, Reinhardt D. Long-term effects of formoterol and salbutamol on bronchial hyperreactivity and beta-adrenoceptor density on lymphocytes in children with bronchial asthma. *Eur J Med Res* 1996;1:465-70.
37. Pao CS, McKenzie SA. Randomized controlled trial of fluticasone in preschool children with intermittent wheeze. *Am J Respir Crit Care Med* 2002;166:945-9.
38. Nielsen KG, Bisgaard H. Bronchodilation and bronchoprotection in asthmatic preschool children from formoterol administered by mechanically actuated dry-powder inhaler and spacer. *Am J Respir Crit Care Med* 2001;164:256-9.
39. Szeffler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, Zeiger RS, Larsen G, Spahn JD, Bacharier LB, Bloomberg GR, Guilbert TW, Heldt G, Morgan WJ, Moss MH, Sorkness CA, Taussig LM. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233-42.
40. Stelmach I, Jerzynska J, Kuna P. A randomized, double-blind trial of the effect of treatment with montelukast on bronchial hyperresponsiveness and serum eosinophilic cationic protein (ECP), soluble interleukin 2 receptor (sIL-2R), IL-4, and soluble intercellular adhesion molecule 1 (sICAM-1) in children with asthma. *J Allergy Clin Immunol* 2002;109:257-63.
41. O'Byrne PM, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A,

- Lamm CJ, Pauwels RA. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. *Chest*. 2006 ;129:1478-85.
42. Reiss TF, Sorkness CA, Stricker W, Botto A, Busse WW, Kundu S, Zhang J. Effects of montelukast (MK-0476); a potent cysteinyl leukotriene receptor antagonist, on bronchodilation in asthmatic subjects treated with and without inhaled corticosteroids. *Thorax* 1997;52:45-8.
43. Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, de Boeck K. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol* 2002;34:342-50.
44. Stelmach I, Majak P, Jerzynska J, Kuna P. The effect of treatment with montelukast on in vitro interleukin-10 production of mononuclear cells of children with asthma. *Clin Exp Allergy* 2005 ;35:213-20.
45. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, Becker A. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. Pediatric Montelukast Study Group. *JAMA* 1998;279:1181-6.
46. Tonelli M, Zignoni M, Bacci E, Dente FL, Di Franco A, Giannini D, Taccola M, Vagaggini B, Paggiaro PL. Short-term effect of the addition of leukotriene receptor antagonists to the current therapy in severe asthmatics. *Pulm Pharmacol Ther* 2003;16:237-40.
47. Nieto A, Pamies R, Oliver F, Medina A, Caballero L, Mazon A. Montelukast improves pulmonary function measured by impulse oscillometry in children with asthma (Mio study). *Respir Med* 2006: 100:1180-85.

48. Currie GP, Lee DK, Dempsey OJ, Fowler SJ, Cowan LM, Lipworth BJ. A proof of concept study to evaluate putative benefits of montelukast in moderate persistent asthmatics. *Br J Clin Pharmacol* 2003 ;55:609-15.
49. Cengizlier R, Demirpolat E, Tulek N, Cakmak F. Circulating ICAM-1 levels in bronchial asthma and the effect of inhaled corticosteroids. *Ann Allergy Asthma Immunol.* 2000;84:539-41.
50. Shapiro GG, Mendelson LM, Pearlman DS. Once-daily budesonide inhalation powder (Pulmicort Turbuhaler) maintains pulmonary function and symptoms of asthmatic children previously receiving inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2001;86:633-40.
51. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162:1500-6.
52. Spahn JD, Covar RA, Jain N, Gleason M, Shimamoto R, Szeffler SJ, Gelfand EW. Effect of montelukast on peripheral airflow obstruction in children with asthma. *Ann Allergy Asthma Immunol.* 2006 ;96:541-9.
53. Tomac N, Tuncer A, Saraclar Y, Adalioglu G. Efficacy of salmeterol in the treatment of childhood asthma. *Acta Paediatr Jpn* 1996;38:489-94.

Legends

Figure 1

Flow chart for the study.

Figure 2

Change from baseline in FEV₁, Rint and SRaw after 4 weeks treatment of budesonide, montelukast, budesonide with montelukast, budesonide with formoterol, and placebo. Data are presented as % change from baseline in each patients (A) and mean with 95% confidence intervals (B). Difference in changes with active treatment between groups is indicated as ANOVA.

Definition of abbreviations: %=percentage of change from baseline; B=budesonide group M=montelukast group; B+ M=budesonide with montelukast group; B+ F=budesonide with formoterol group

Figure 3

Change from baseline in FEF₂₅₋₇₅ after 4 weeks treatment of budesonide, montelukast, budesonide with montelukast, budesonide with formoterol, and placebo. Data are presented as % change from baseline in each patients (A) and mean with 95% confidence intervals (B). Difference in changes with active treatment between groups is indicated as ANOVA.

Definition of abbreviations: %=percentage of change from baseline; B=budesonide group M=montelukast group; B+ M=budesonide with montelukast group; B+ F=budesonide with formoterol group

Table 1

Patients baseline characteristics. Data is presented as mean and standard error mean.

Definition of abbreviations: NS= not statistically significant; % pred.=percentage of predicted value

Table 2

Effect of treatment with budesonide, montelukast, budesonide with montelukast, budesonide with formoterol, placebo on FEV₁, FEF_{25-75%}, SRaw and Rint. Values are expressed as means with standard error mean (SEM).

Definition of abbreviations: FEV₁=forced expiratory volume in one second; FEF_{25-75%}=forced expiratory flow between 25% and 75% of the vital capacity; SRaw=specific airway resistance; Rint=resistance by the interrupter technique; % pred.= percentage of predicted value.

Table 1

	budesonid e N=29	monteluka st N=29	budesonid e + monteluka st N=29	budesonid e + formoterol N=29	placebo N=27	P
Age [years]	12±3.1	10.4±2.9	11±3.2	8.79±2.4	11.4±3.3	N S
Male children [%]	69	62.1	69	58.6	70.4	N S
Duration of asthma [years]	3.97±0.52	3.85±0.61	3.79±0.58	3.93±0.63	3.88±0.47	N S
FEV1 pred.] [%]	94.4±1.8	95.5±2.1	94.8±2.1	93.1±2.3	94.8±1.8	N S

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Table 2

		Before		After		P
		Mean	SEM	Mean	SEM	
budesonide	FEV ₁ [% pred.]	94.4	1.8	97.2	1.9	0.008
	FEF25-75 [%]	90.4	6.9	92.9	5.4	0.529
	SRaw [% pred.]	172.2	6.3	157.6	7.1	0.048
	Rint [% pred.]	128.6	5.0	120.5	4.8	0.009
montelukast	FEV ₁ [% pred.]	95.5	2.1	97.9	1.8	0.028
	FEF25-75 [%]	91.3	6.8	97.8	5.2	0.048
	SRaw [% pred.]	167.1	10.3	157.8	7.1	<0.001
	Rint [% pred.]	134.5	6.4	126.0	5.3	0.003
budesonide +	FEV ₁ [% pred.]	94.8	2.1	100.2	1.9	<0.001
	FEF25-75 [%]	90.4	6.4	98.2	4.6	0.018
montelukast	SRaw [% pred.]	170.2	7.4	149.3	5.7	0.001
	Rint [% pred.]	132.9	4.0	112.9	2.9	<0.001
budesonide + formoterol	FEV ₁ [% pred.]	93.1	2.3	98.3	2.2	0.002
	FEF25-75 [%]	98.5	5.3	96.5	5.0	0.616
	SRaw [% pred.]	175.6	5.9	157.2	7.3	0.001
	Rint [% pred.]	128.3	3.3	109.4	2.8	<0.001
placebo	FEV ₁ [% pred.]	94.8	1.8	90.3	1.6	0.005
	FEF25-75 [%]	98.5	6.5	90.6	7.8	0.007
	SRaw [% pred.]	166.0	6.2	183.0	5.5	0.002
	Rint [% pred.]	127.9	7.3	134.0	7.8	0.008

Figure 1:

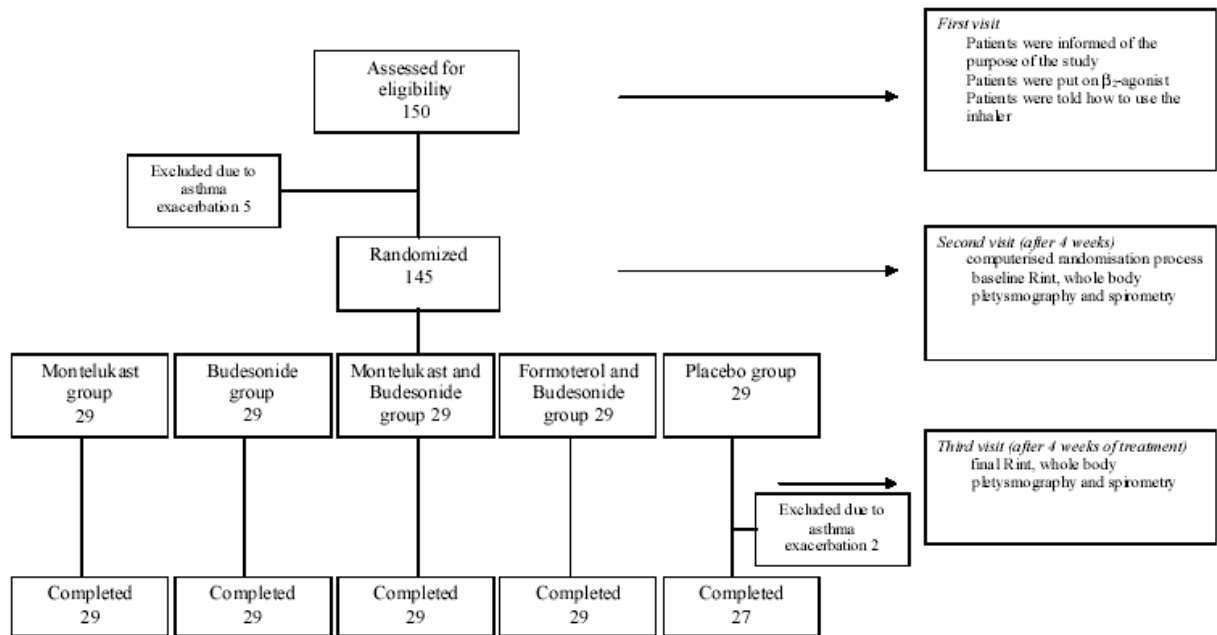


Figure 2:

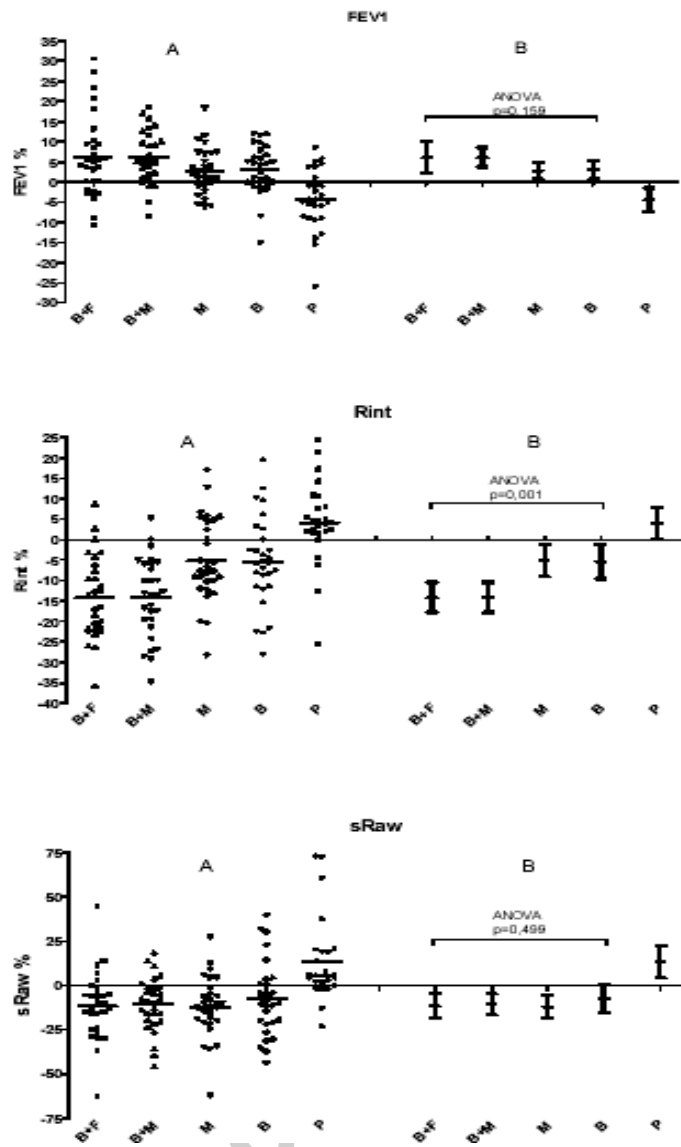
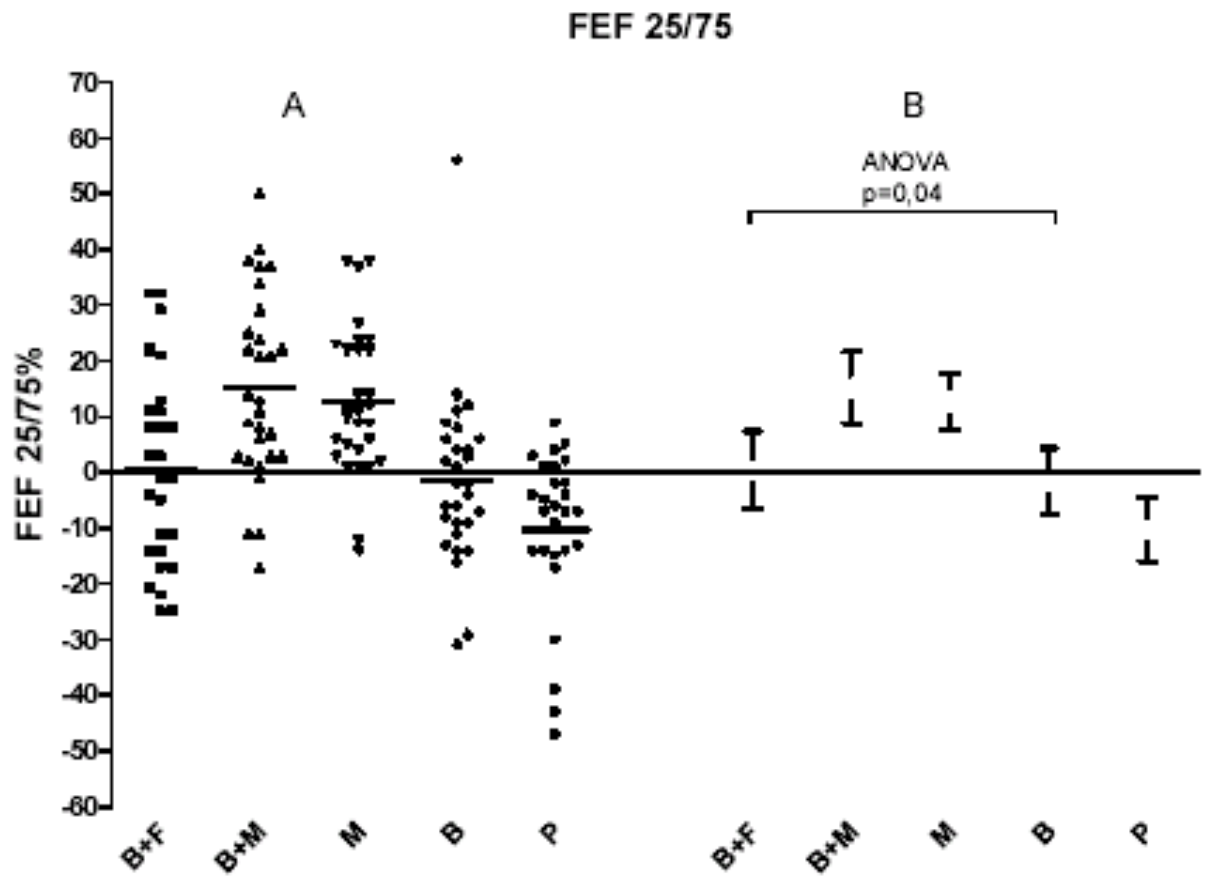


Figure 3:



Accepted