Respiratory Medicine (2006) **100**, 1180–1185

respiratoryMEDICINE

Montelukast improves pulmonary function measured by impulse oscillometry in children with asthma (Mio study)

Antonio Nieto[a,*], Rafael Pamies[a], Fernando Oliver[a], Alejandra Medina[b], Luis Caballero[a], Angel Mazon[a]

[a]*Pediatric Allergy Unit, Children's Hospital, Av. Campanar 21, Valencia 46009, Spain*
[b]*Pediatric Allergy Unit, Hospital de Querétaro, México*

Received 13 October 2005; accepted 25 October 2005

KEYWORDS
Asthma;
Antileukotrienes;
Airway resistance;
Reactance

Summary
Background: 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. The impulse oscillometry (IOS) technique is useful to evaluate both central and peripheral airways function.
Objective: To measure the effect of oral montelukast on airways resistance evaluated by oscillometry in children with asthma.
Methods: In an open study, respiratory function in 23 children with mild asthma and a positive bronchodilator response was assessed by spirometry and oscillometry. They took oral montelukast during 4 weeks and were again evaluated. As a control group, 23 similar patients with no preventive treatment underwent the same study.
Measurements and main results: Children on oral montelukast showed improvements (measured in $kPa\,s\,L^{-1}$) in all oscillometry parameters: mean 0.20 (22.4%) in total respiratory impedance Zrs5, 0.18 (21.8%) in total airway resistance Rrs5, 0.09 (17.8%) in central airway resistance Rrs20, and 0.09 (28.8%) in distal capacitive reactance Xrs5; the frequency of resonance Fres improved 2.3 Hz (8.7%) ($P<0.05$ in all cases). No changes were found in the control group. Expiratory flows showed no changes except for a small ($0.23\,L\,s^{-1}$, 7.4%) but significant worsening of FEF25–75 in the control group.
Conclusions: Montelukast improves central and especially peripheral airways function in the first month of treatment, as evaluated by IOS, a technique based on tidal breathing analysis which is more sensitive than conventional forced spirometry.

*Corresponding author. Tel.: +34 96 1973258; fax: +34 96 1973258.
E-mail address: nieto_ant@gva.es (A. Nieto).

0954-6111/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2005.10.025

Introduction

The inflammation of airways is the underlying pathogenetic mechanism of asthma. This inflammation usually affects the whole respiratory tract, from the nose down to the most distal airways and alveolar tissue.[1–4] The peripheral airways have been called the ''silent zone'', due to the paucity of non-invasive methods to evaluate their function and condition. Nevertheless, they have been recognized as a crucial site responsible for many of the most relevant pathophysiologic features of asthma.[5–11] Additionally, it has been pointed out that inhaled medication hardly reaches these peripheral airways, and that an alternative would be the use of systemic anti-inflammatory approaches.[2,4]

The inflammation of airways gives rise to bronchial hyperreactivity and to increases of resistance to airflow, hence functional respiratory studies are used as surrogate evaluators of inflammation. Impulse oscillometry (IOS) is quite a recent technique which allows for respiratory functional studies, without forced maneuvers, performed at spontaneous breathing and therefore requires minimal cooperation. Thus, respiratory function can be studied in small children, even as young as 3–6 years. The IOS technique measures changes in airway impedance while the device emits impulse shaped sound signals which contain frequencies at various wavelengths. The main parameters thus obtained reflect the total pulmonary impedance (Zrs5), the total respiratory resistance (Rrs5), the central airways resistance (Rrs20), the distal capacitive reactance (Xrs5), and the frequency of resonance (Fres).[12] As there is nearly no measurable resistance in the peripheral compartments of the lung, the elastic properties are indirect indicators of peripheral obstruction, expressed in a negative shift of the parameter Xrs5.

There are studies evaluating the response to bronchodilators or inhaled steroids with the IOS technique, but there is none, to our knowledge, evaluating the effect of antileukotrienes. The aim of our work was to study the effect of montelukast on the IOS parameters, to evaluate the impact of this drug in children with mild asthma, since these parameters have been recognized as indirect measures of the inflammation of the airways. The main endpoint was the change in Xrs5, because it has been proposed as representative of the inflammation of the distal airways.[13]

Methods

We performed an open study, in which 46 children with mild asthma were randomized to receive montelukast or no preventive treatment during 4 weeks. The inclusion criteria were: age over 5 years, three or more episodes of asthma in the previous year, no symptoms at the time of the study, no use of antiasthmatic medication in the previous month, $FEV_1 > 80\%$ of predicted, and a baseline bronchodilating response of at least one of the following: increase of $>12\%$ in FEV_1, $>12\%$ in PEF, $>25\%$ in FEF25–75, $>25\%$ in Xrs5, decrease of $>25\%$ in Rrs5.

An IOS and spirometry study was done, according to the ERS Task Force recommendations.[14] For IOS, a Jaeger MasterScreen Impulse Oscillometry System (Jaeger Co, Wurzburg, Germany) was used. In brief, the child spontaneously breathes during 30 s throughout the IOS head, with a nose clip and pressing his/her cheeks with both hands, while a loudspeaker in the head of the system emits sound impulses every 0.2 s. These pressure fluctuations are superimposed on the breathing pattern and measured as central flow with the help of a Lilly type pneumotachograph, and as mouth pressure with a differential pressure transducer, and they are fed into a fast Fourier transformation. The relation of pressure and flow signal permits measurement of impedance of the total respiratory system (Zrs5), and from this, the total (Rrs5) and the central (Rrs20) airways resistances, and the reactance (Xrs5) can be calculated.[15] The number in the parenthesis indicates the wavelength at which measures are made. The point where the usually negative reactance reaches 0, measured in Hertz, is called the frequency of resonance (Fres). The Xrs5 reactance best represents the condition of peripheral airways. Also, as Rrs5 is thought to reflect total airway resistance and Rrs20 proximal resistance, the difference Rrs5−Rrs20 might be used as a surrogate of the resistance of the small airways. The reference values of Duiverman were used for those below 6 years.[16] From 7 years reference values of Berdel/Lechtenboerger were available (data not published). For spirometry, a pneumotachometer system (MasterScreen Pneumo Jaeger, Wurzburg, Germany) was used. The best flow-volume curve, from at least three trials was selected, according to ATS criteria modified by Arets et al.[17] and Eigen et al.[18] The reference values of Zapletal et al. were used.[19] Two inhalations of salbutamol 100 mcg were administered through a spacer device, and the bronchodilating response was assessed 20 min later with IOS and spirometry.

A prescription of montelukast (Merck, New Jersey, USA) was made at the first visit, and patients were instructed to take montelukast once a day (4 mg when under 6 years, 5 mg for those

between 6 and 14 years, 10 mg for those above), every evening during 4 weeks, and the same functional respiratory study was repeated thereafter. Compliance of treatment was evaluated by interviewing patients and parents. The control group of patients, in whom the preventive treatment was delayed for 1 month, underwent the same tests. The study was approved by the local Ethics Committee, and informed consent was obtained from parents and older children.

Statistical study

The C-4 Study Design Pack (GSK) was used to calculate the sample size for paired data, with an α-error of 0.05 and a β-error of 0.1, to detect a change of 20% in the main variable (Xrs5) and also a change of 15% in FEV_1 and FEF25–75. The statistical analysis was performed with the SPSS 10.0 statistical package (SPSS Inc., Chicago, IL, USA). Comparisons of data, separated for active and control group, between first and second visit were assessed with paired *T*-test, or its equivalent non-parametric Wilcoxon rank test for data with non-normal distribution. Values of $P<0.05$ were considered as significant.

Results

Both the active and the control groups included 23 children each. As shown in Table 1, no statistical difference at baseline for demographic and functional characteristics was found. Besides the absolute figures, the percentages of predicted values, depicted in Table 2, were similar for the two groups, as well as the bronchodilating response at baseline (not shown). The number of patients fulfilling the basal bronchodilating response criteria for inclusion did not differ between the active and the control group, and were respectively, 4 and 5, for improvement in FEV_1, 10 and 6 in PEF, 8 and 10 in FEF 25–75, 14 and 9 in Rrs5, and 16 and 12 in Xrs5 ($P>0.1$ in all).

The difference for functional data between the first and the second visit, after four weeks, can be seen in Table 3 for both control and active groups. No change was seen in the IOS parameters in the control group; there was a trend for worsening in the spirometry data, which was small but statistically significant for FEF25–75. By contrast, in the montelukast group we found a significant improvement in all IOS parameters, especially in reactance Xrs5, whose change is shown in Fig. 1. There was a trend for improvement also in the spirometry data, especially for FEF25-75, although not to a significant degree.

Discussion

Most of the resistance of the airways to airflow depends on the proximal bronchi, so it is difficult to assess increases of the resistance of the low airway. Nevertheless, several clinical features have been proposed as correlates of the small airways

Table 1 Baseline demographic and functional characteristics; results in absolute units.

	Control group ($n=23$)	Montelukast group ($n=23$)
Gender (F/M)	10/13	11/12
Age (years)	9.74 ± 2.76	9.68 ± 3.01
Age: <6/6–14/>14 years	3/19/1	3*/19†/1‡
Duration of asthma (years)	5.3 ± 2.7	5.8 ± 3.3
Weight (kg)	37.66 ± 15.98	40.17 ± 14.24
Height (cm)	137.9 ± 16.3	138.4 ± 17.3
FEV_1 (L)	2.09 ± 0.63	2.14 ± 0.74
PEF ($L\,s^{-1}$)	4.29 ± 1.27	4.52 ± 1.69
FEF25–75 ($L\,s^{-1}$)	2.34 ± 0.88	2.48 ± 1.14
Zrs5 ($kPa\,s\,L^{-1}$)	0.87 ± 0.22	0.89 ± 0.25
Rrs5 ($kPa\,s\,L^{-1}$)	0.81 ± 0.21	0.83 ± 0.24
Rrs20 ($kPa\,s\,L^{-1}$)	0.54 ± 0.15	0.52 ± 0.14
Rrs5−Rrs20 ($kPa\,s\,L^{-1}$)	0.27 ± 0.18	0.31 ± 0.20
Xrs5 ($kPa\,s\,L^{-1}$)	-0.28 ± 0.11	-0.31 ± 0.12
Fres (Hz)	20.3 ± 4.5	21.9 ± 3.3

P: non-significant for all data.
Dose of montelukast: *4 mg/day; †5 mg/day; ‡10 mg/day.
Fres: Frequency of resonance.

Table 2 Baseline functional parameters, in percentage of predicted.

	Control group	Montelukast group
FEV_1 (%)	106.9±10.7	109.5±15.9
PEF (%)	94.9±12.67	99.9±19.18
FEF25–75 (%)	93.9±25.9	99.4±30.6
Zrs5 (%)	115.7±23.9	117.6±22.6
Rrs5 (%)	115.57±23.35	116.79±22.72
Rrs20 (%)	103±30.1	96.25±27.69
Xrs5 (%)	116.5±39.3	125.8±33.2

P: non-significant for all data.

Table 3 Mean increases or decreases (negative sign) in absolute values (% in parenthesis) from the first to the second visit.

	Control group	Montelukast group
FEV_1 (L)	−0.06 (−2%)	0.04 (2.9%)
PEF ($L\,s^{-1}$)	−0.22 (−4.5%)	0.03 (3.9%)
FEF25–75 ($L\,s^{-1}$)	−0.23 (−7.4%)*	0.17 (10.9%)†
Zrs5 ($kPa\,s\,L^{-1}$)	−0.034 (−3.9%)	−0.20 (−22.4%)‡
Rrs5 ($kPa\,s\,L^{-1}$)	−0.036 (−4.5%)	−0.18 (−21.8%)‡
Rrs20 ($kPa\,s\,L^{-1}$)	−0.02 (3.7%)	−0.09 (−17.8%)‡
Rrs5−Rrs20 ($kPa\,s\,L^{-1}$)	−0.017 (−0.52%)	−0.089 (−13.6%)¶
Xrs5 ($kPa\,s\,L^{-1}$)§	−0.0009 (−0.3%)	0.09 (28.8%)‡
Fres (Hz)	0.44 (4.3%)	−2.3 (−8.7%)#

Comparisons within group with baseline:
*$P = 0.035$. †$P = 0.11$. ‡$P < 0.001$. ¶$P = 0.005$. #$P = 0.025$. All the rest: $P > 0.20$.
§:As Xrs5 reactance has usually negative values, increases are associated with improvement.
Fres: Frequency of resonance.

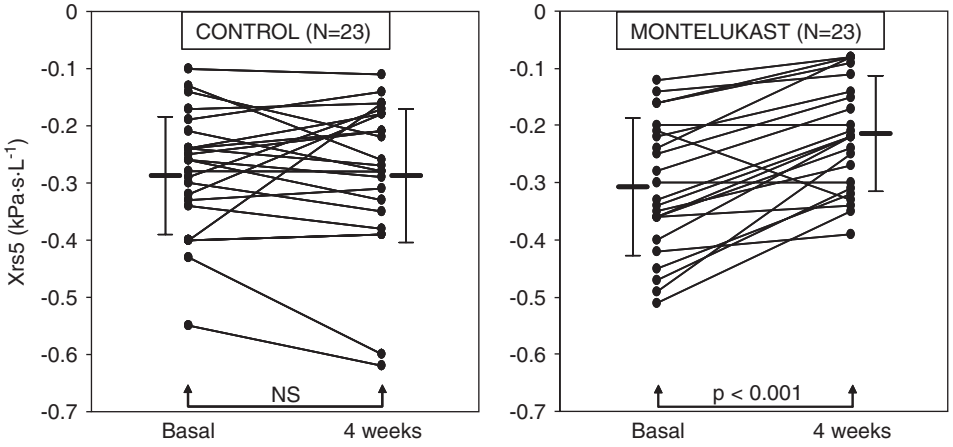

Figure 1 Increases in capacitive reactance Xrs5 in the control and in the montelukast group.

condition, namely nocturnal asthma,[7,20,21] cold air and exercise-induced asthma,[22] asthma exacerbations,[23] and persistent wheezing in children.[24] In conventional spirometry, it is commonly accepted that the mid-expiratory flows best reflect the function of the small caliber airways. However, the requirement of forced expiratory maneuvers makes its evaluation difficult, especially in younger patients, and other methods have been developed for assessment of their function.

The technique of IOS takes advantage of the changes in airflow when the airways are subjected to sound impulses. These changes with different wavelength impulses are measured to calculate

resistance to airflow: thus, at 5 Hz wavelength, the total system impedance (Zrs5), the total airway resistance (Rrs5) and the peripheral capacitive reactance (Xrs5) can be estimated, while the large caliber airway resistance (Rrs20) is best assessed at 20 Hz wavelength.[25–27] Changes in airway resistance usually precede changes in airflow, and it has been estimated that at least increases of 40–50% in airway resistance are comparable to a decrease of 20% detected in spirometry studies.[28–30] The IOS technique is, hence, more sensitive to recognize the early subtle changes in the airways arising from the underlying inflammation of asthma. In fact, at low oscillation frequencies, elastic elements in peripheral airways are the dominant reactant to applied pressure, and reflect small airway mechanical properties. In airway obstruction, small airways are functionally obstructed, due to peripheral airway inflammation. Accordingly, changes in low-frequency Xrs rather reflect peripheral airway disease.[13] This, together with the ease of performing the technique makes IOS a very valuable tool for the assessment and follow-up of asthma, especially in children.

Inhaled corticosteroids are the most potent anti-inflammatory drugs used for treatment of asthma, but there is concern about their side effects. Additionally, in patients with bronchial obstruction inhaled drugs hardly reach the peripheral airways and the distribution of aerosol is uneven and predominant in the large central airways.[31,32] Leukotriene receptor antagonists, such as montelukast, have a lower anti-inflammatory effect, but a better safety profile, and since they are orally given, they can reach the whole airways. This confers them a special advantage for the treatment of distal airways disease.

In our study montelukast decreased all measured IOS parameters, in the first month of treatment. Improvements were found in parameters evaluating the whole (Zrs5 and Rrs5), the central (Rrs20) and the distal airways (Rrs5—Rrs20 and Xrs5) function, but were most marked for the latter. There was a moderate, though not significant, improvement for the FEF25–75, in accordance with its ability to evaluate small airways function. As expected, no effect was seen in the control group, except for a small but significant worsening of the FEF25–75.

Both groups were comparable at baseline, and the end-point was an objective measure, so, even though it was an open study, the bias should be limited. The variability of the IOS technique, estimated at around 10.5%,[33] could weaken our findings, but the striking differences between the groups reinforce them, especially when considering that the number of patients in each group was not large. The conditions of the study were those of real life, thus results should be more applicable to the common asthmatic patients.

Our patients had mild persistent asthma and had no symptoms at the time of the study, but they had a positive bronchodilating test and their airways resistance decreased with preventive treatment, thus disclosing a subclinical inflammation of the airways. This bronchial subclinical inflammation has been described in asymptomatic asthmatic patients,[34,35] and, using sophisticated methods, physiologic abnormalities have been demonstrated in the peripheral airways of asymptomatic adult patients with mild asthma and normal conventional lung function tests.[5] Current guidelines do not recommend preventive treatment for patients with mild intermittent asthma, but studies are warranted to evaluate the degree of involvement of airways and their response to anti-inflammatory therapy. This could eventually justify the use of preventive treatment able to reach the peripheral airways in these patients, even though they are asymptomatic.

In conclusion, this study demonstrates the decrease of airways resistance by the therapy with oral montelukast in asthmatic children, as measured by IOS. This effect was found in the whole airway, but was more pronounced on the distal bronchi. It appeared after a short period of only one month of treatment. The role of montelukast in the treatment of adult and childhood asthma remains to be well established. Issues such as clinical effectiveness, compliance, cost, side effects and long-term outcome must be considered. Our data provide evidence that, at least in the short term, montelukast can reduce airway resistance, one of the major pathophysiologic mechanisms of asthma.

Acknowledgment

We thank Dipl.Ing. H.J. Smith for reviewing the technical description of IOS.

References

1. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;**111**: 1171–83.
2. Bjermer L. History and future perspectives of treating asthma as a systemic and small airways disease. *Respir Med* 2001;**95**:703–19.
3. Tulic MK, Christodoulopoulos P, Hamid Q. Small airway inflammation in asthma. *Respir Res* 2001;**2**:333–9.

4. Martin RJ. Therapeutic significance of distal airway inflammation in asthma. *J Allergy Clin Immunol* 2002;**109**:S447–60.
5. Wagner EM, Liu MC, Weinmann GG, et al. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis* 1990;**141**:584–8.
6. Kraft M, Djukanovic R, Wilson S, et al. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996;**154**:1505–10.
7. Kraft M, Martin RJ, Wilson S, et al. Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma. *Am J Respir Crit Care Med* 1999;**159**:228–34.
8. Hamid Q, Song Y, Kotsimbos TC, et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997;**100**:44–51.
9. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. *Eur Respir J* 1997;**10**:292–300.
10. Haley KJ, Sunday ME, Wiggs BR, et al. Inflammatory cell distribution within and along asthmatic airways. *Am J Respir Crit Care Med* 1998;**158**:565–72.
11. Minshall EM, Hogg JC, Hamid QA. Cytokine mRNA expression in asthma is not restricted to the large airways. *J Allergy Clin Immunol* 1998;**101**:386–90.
12. Vogel J, Smidt U. *Impulse oscillometry*. Frankfurt Main: pmi Verlagsgruppe GmbH; 1994.
13. Smith H, Reinhold P, Goldman M. Forced oscillation technique and impulse oscillometry. *Eur Respir Mon* 2005;**31**:72–105.
14. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003;**22**:1026–41.
15. Bisgaard H, Klug B. Lung function measurement in awake young children. *Eur Respir J* 1995;**8**:2067–75.
16. Duiverman EJ, Clement J, van de Woestijne KP, et al. Forced oscillation technique. Reference values for resistance and reactance over a frequency spectrum of 2–26 Hz in healthy children aged 2.3–12.5 years. *Bull Eur Physiopathol Respir* 1985;**21**:171–8.
17. Arets HG, Brackel HJ, van der Ent CK. Forced expiratory manoeuvres in children: do they meet ATS and ERS criteria for spirometry? *Eur Respir J* 2001;**18**:655–60.
18. Eigen H, Bieler H, Grant D, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med* 2001;**163**:619–23.
19. Zapletal A, Zamenek M, Paul T. *Lung function in children and adolescents: methods and reference values*. Basel: Herzog; 1987.
20. Irvin CG, Pak J, Martin RJ. Airway-parenchyma uncoupling in nocturnal asthma. *Am J Respir Crit Care Med* 2000;**161**:50–6.
21. Kraft M, Pak J, Martin RJ, et al. Distal lung dysfunction at night in nocturnal asthma. *Am J Respir Crit Care Med* 2001;**163**:1551–6.
22. Kaminsky DA, Bates JH, Irvin CG. Effects of cool, dry air stimulation on peripheral lung mechanics in asthma. *Am J Respir Crit Care Med* 2000;**162**:179–86.
23. in't Veen JC, Beekman AJ, Bel EH, et al. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *Am J Respir Crit Care Med* 2000;**161**:1902–6.
24. Krawiec ME, Westcott JY, Chu HW, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;**163**: 1338–43.
25. Pride NB. Forced oscillation techniques for measuring mechanical properties of the respiratory system. *Thorax* 1992;**47**:317–20.
26. Ritz T, Dahme B, Dubois AB, et al. Guidelines for mechanical lung function measurements in psychophysiology. *Psychophysiology* 2002;**39**:546–67.
27. Wouters EF, Polko AH, Schouten HJ, et al. Contribution of impedance measurement of the respiratory system to bronchial challenge tests. *J Asthma* 1988;**25**:259–67.
28. van Noord JA, Clement J, van de Woestijne KP, et al. Total respiratory resistance and reactance as a measurement of response to bronchial challenge with histamine. *Am Rev Respir Dis* 1989;**139**:921–6.
29. Bouaziz N, Beyaert C, Gauthier R, et al. Respiratory system reactance as an indicator of the intrathoracic airway response to methacholine in children. *Pediatr Pulmonol* 1996;**22**:7–13.
30. Duiverman EJ, Neijens HJ, Van der Snee-van Smaalen M, et al. Comparison of forced oscillometry and forced expirations for measuring dose-related responses to inhaled methacholine in asthmatic children. *Bull Eur Physiopathol Respir* 1986;**22**:433–6.
31. Esmailpour N, Hogger P, Rabe KF, et al. Distribution of inhaled fluticasone propionate between human lung tissue and serum in vivo. *Eur Respir J* 1997;**10**:1496–9.
32. Laube BL, Swift DL, Wagner Jr HN, et al. The effect of bronchial obstruction on central airway deposition of a saline aerosol in patients with asthma. *Am Rev Respir Dis* 1986;**133**:740–3.
33. Ortiz G, Menendez R. The effects of inhaled albuterol and salmeterol in 2- to 5-year-old asthmatic children as measured by impulse oscillometry. *J Asthma* 2002;**39**: 531–6.
34. de Kluijver J, Evertse CE, Schrumpf JA, et al. Asymptomatic worsening of airway inflammation during low-dose allergen exposure in asthma: protection by inhaled steroids. *Am J Respir Crit Care Med* 2002;**166**:294–300.
35. Obase Y, Shimoda T, Kawano T, et al. Bronchial hyperresponsiveness and airway inflammation in adolescents with asymptomatic childhood asthma. *Allergy* 2003;**58**: 213–20.