

Effect of montelukast on exhaled NO in asthmatic children exposed to relevant allergens

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The level of exhaled nitric oxide (FENO) is increased in house dust mite (HDM)-sensitized asthmatic children after exposure to HDM antigen, and inhaled steroids can prevent this increase. The aim of this study was to evaluate whether montelukast could prevent an increase in FENO levels in allergic asthmatic children after a brief period of exposure to relevant allergens. Sixteen children were evaluated at the residential house 'Istituto Pio XII' (Misurina, Belluno, Italy) in the Italian Alps, a dust mite-free environment. FENO levels were evaluated before (t_0) and immediately after (t_1) the children were exposed to HDM allergens for 2 weeks in their homes at sea level. No significant difference in FENO was observed in the fluticasone-treated group of children after 2 weeks at sea level. In the group treated with montelukast, an increase in FENO was observed between t_0 and t_1 , which failed to reach statistical significance. These preliminary data suggest that oral montelukast could be effective in preventing the relapse in airway inflammation in allergic asthmatic children who are occasionally exposed to relevant allergens for a short period of time.

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The leukotriene receptor antagonist, montelukast, has been demonstrated to be effective in reducing the level of exhaled nitric oxide (FENO) in asthmatic children (1,2). As FENO is currently regarded as a non-invasive means for assessing airway inflammation in asthma (3), it was concluded (1,2) that there was a potential anti-inflammatory role of leukotriene antagonists in the treatment of bronchial asthma.

In recent studies we have observed that the FENO level is elevated after a short period of natural exposure to house dust mite (HDM) antigen in HDM-sensitized asthmatic children (4), and that inhaled steroids can prevent this increase (5).

In this study we evaluated whether treatment with oral montelukast can be effective in preventing the expected increase in FENO levels after a

brief period of exposure to relevant allergens in a group of asthmatic children allergic to HDM.

Materials and methods

Subjects

Sixteen children (age-range 6–13 years) with a history of mild bronchial asthma, a positive skin-prick test to HDM, and a history of asthma related to exposure to HDM, were evaluated at the residential house 'Istituto Pio XII' (Misurina, Belluno, Italy), situated 1756 m above sea level in the Italian Alps. The relevance of HDM avoidance for asthma control in this group of children was demonstrated by the fact that it was possible to withhold all the regular drug treatments during

the stay in the HDM-free environment. None of the patients had reported respiratory infections for at least 2 months before the start of the study and none was allergic to furred pets. None of the children had received oral corticosteroids for at least 2 months, and inhaled corticosteroids for at least 1 month, prior to the start of the study as they were staying in HDM-free environment.

The study was approved by the Istituto Pio XII Ethics Committee, and both children and their parents gave informed consent.

Study design

This was a pilot study with an open design. The children admitted to the study had been living at the Istituto Pio XII (an environment free of HDM allergen because of its high-altitude location) for at least 3 months at the time of admission to the study (t_0). FENO levels were evaluated before (t_0) and immediately after (t_1) the children spent a 2-week Christmas holiday in their homes at sea level, where they were assumed to be exposed to HDM allergens. This study was performed out of the pollen season in order to avoid interference of outdoor allergens in those patients who were also sensitized to pollens.

Patients were randomly divided into two groups: one group received montelukast (5 mg daily); the other group received inhaled fluticasone (100 µg twice daily). Inhaled β_2 agonists were allowed as required. Treatment with the study drugs was initiated the day the children left the residential house, after t_0 , and was maintained during the study period.

FENO measurement

FENO was measured by using a chemiluminescence analyzer (Logan LR 2149; Rochester, Kent, UK) (6,7). Briefly, the subjects were asked to perform a single slow exhalation starting from total lung capacity (TLC) through a mouthpiece, against a resistance (mouth pressure >5 mm H₂O), and with a biofeedback used to maintain a 5–6 l/min steady flow in order to separate the nasopharynx from the oropharynx by the soft palate, hence preventing the contamination of FENO with nasal NO. This method has been shown to be successfully applicable both in adults and in children. The NO value was measured at the plateau of the end-exhaled reading and expressed in parts per billion (p.p.b.), according to previous guidelines (8).

FENO determinations were always performed by the same investigator (A.L.) who was unaware of the treatment regimen prescribed to the patients.

The levels of FENO evaluated at t_0 and t_1 were statistically compared within groups by the Wilcoxon test and between groups by the Mann–Whitney *U*-test.

Measurement of mite allergen levels.

Parents were asked to collect dust from the mattresses of the subjects participating the study. Dust collection was performed in a standardized manner, by vacuuming the mattress surface for an approximate area of 2 m² for 5 min (9) using a vacuum cleaner fitted with a new bag. Bags containing samples were stored in a sealed plastic bag at 4°C until the dust was processed for measurement of mite group I allergen levels, which was performed using monoclonal antibodies (mAbs) in a two-site immunometric enzyme-linked immunosorbent assay (ELISA) (10,11).

The results were expressed in µg/g (i.e. µg of mite group I allergens per g of dust) (12).

Results

All of the children completed the study; nine children received montelukast and seven received inhaled fluticasone. The levels of FENO measured at t_0 and t_1 were not significantly different between the two groups of patients. The FENO levels of the montelukast-treated patients increased at t_1 , but this failed to reach statistical significance (Fig. 1).

Group 1 HDM antigen levels were 15.1 ± 8.13 and 17.2 ± 7.57 µg/g of dust in the fluticasone and in the montelukast groups, respectively (p =NS). No relationship was observed between HDM levels and FENO levels.

Discussion

FENO has been demonstrated to be promptly modified by exposure or avoidance of relevant allergens in allergic asthmatic children (4,13). We have previously observed that inhaled steroids are effective in preventing an increase in FENO when children sensitized to HDM and living in the Istituto Pio XII are re-exposed to relevant allergens during a 2-week holiday period at sea level (5). In the present study, the FENO levels in the fluticasone-treated group showed a tendency to decrease after 2 weeks of exposure to HDM, confirming the efficacy of inhaled steroids in controlling and preventing airway inflammation in asthma. In the group treated with montelukast, the observed increase was still not significant. However, from the present data it cannot be excluded that the non-significant difference in the

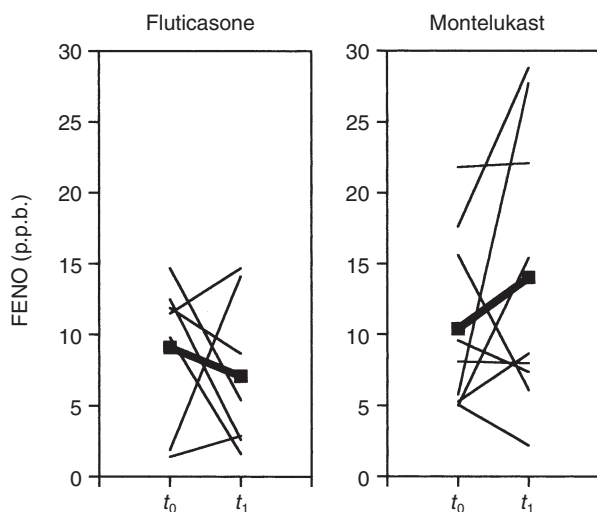


Fig. 1. Exhaled nitric oxide (FENO) individual values before (t_0) and immediately after (t_1) the children spent a 2-week Christmas holiday in their homes, which were located at sea level. Thick lines show mean values.

montelukast group could be the result of a type 2 statistic error owing to the small number of participants in the sample. In this study no placebo group was included as the Ethics Committee objected that the previous data, with a similar experimental design, had already confirmed that even a short period of antigen exposure was responsible for a prompt and significant increase in airway inflammation in asthmatic children not receiving anti-inflammatory therapy (4,5).

The results of this study are consistent with previous publications showing an effect of montelukast on the levels of FENO in asthmatic children (1,2). In particular, in a study by Bratton and co-workers (2) it was observed that montelukast was capable of reducing FENO levels by 20% after 2 weeks of treatment. The authors of this study also showed that the effect of montelukast was rapid, with a 15% fall in FENO levels in the first 2 days of treatment (which was independent of concurrent medications), thus demonstrating a potential anti-inflammatory effect of this class of drug in asthmatic children.

In conclusion, the observations of the present study should be confirmed by further studies with a greater number of subjects and using a double-blind design, with the aim of establishing a benefit of oral montelukast for preventing relapses in airway inflammation in allergic asthmatic children who are occasionally exposed to relevant allergens for a short period of time.

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