The Effect of Beclomethasone Inhalation and Oral Montelukast Sodium on Serum IgE Levels and Clinical Parameters in Asthmatic Children

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Abstract:
IgE is considered to play a crucial role in allergic immune responses. Inhaled steroids and anti-leukotrienes are anti-asthmatic drugs which down regulate the immune responses. The present study was conducted to determine and compare the effects of a 6-months treatment with 600 mcg of inhaled beclomethasone and 5 mg of oral montelukast sodium on serum IgE, forced expiratory volume in 1 s (FEV1) and clinical asthma scores in children with mild to moderate bronchial asthma. Sixty children with mild to moderate persistent asthma and sensitive to house-dust mites were randomly allocated to receive beclomethasone 600 mcg or montelukast 5 mg for 6 months. The level of serum total IgE, clinical parameters and FEV1 were measured before and after treatment. The results proved that, after 6 months of treatment, inhaled beclomethasone and montelukast, significantly decreased serum levels of total IgE, clinical asthma scores and FEV1 (P<0.01, P<0.01 and P<0.05 respectively). There were no significant differences between inhaled beclomethasone and oral montelukast in changes of all clinical parameters, FEV1 and serum total IgE levels.

Conclusion: Both inhaled beclomethasone and oral montelukast decreased the serum IgE levels and improved the clinical parameters and pulmonary function in asthmatic children.

Introduction:
Bronchial asthma is the most common chronic lung disease in children.1 It is now clear that asthmatic patients have obvious inflammatory changes in their airways.2 T cells and mast cells secrete an array of cytokines which direct eosinophil growth and maturation and promote the isotype switching of B lymphocytes from IgM to IgE.3 Increased levels of total IgE has been shown to be associated with bronchial asthma prevalence.4 In a survey of more than 800 patients, elevated serum IgE levels were associated with a three fold increase in bronchial hyperresponsiveness, independently of the presence of asthma symptoms or specific IgE.5 Since allergic factors play a role in more than 90% of pediatric patients with asthma,6 there are advantages to treatments that may reduce IgE levels. There is evidence that in asthmatic patients IgE levels might be affected by inhaled corticosteroids7 and anti-leukotrienes.8 Inhaled corticosteroids are often recommended as initial controller therapy for the management of persistent asthma because of their anti-inflammatory effects.9 Some studies showed that inhaled corticosteroids were able to reduce serum IgE in asthmatic children.10 However, the inhaled form of drug delivery is associated with lower adherence to therapy compared with that seen with drug delivered by means of the oral route and many patients experience difficulty in using inhaled therapy.11,12 Several large clinical trials in adults with chronic asthma have documented that oral montelukast, a leukotriene receptor antagonist, improved asthma symptoms and lung functions13,14 and also, decreased serum levels of interleukin 4,15 essential for IgE synthesis. Additionally, studies in asthmatic adults and children have demonstrated that adherence to therapy is substantially greater with oral montelukast than with inhaled asthma therapy.16,17

The aim of the present study was to determine and compare the effects of 6 months of treatment with inhaled corticosteroid (beclomethasone) and single oral dose of the leukotriene receptor antagonist (montelukast) on serum IgE levels, forced expiratory volume in 1 s (FEV1) and clinical asthma scores in children with mild to moderate persistent asthma.

Subjects and Methods:
Sixty children aged 6–12 years with mild to moderate persistent asthma and sensitive to house-dust mites (Dermatophagoides pteronyssinus) who were newly attending Asthma Clinic, King Saud Hospital, Qassim, Kingdom Saudi Arabia, participated in this study. Asthma was defined in accordance with published criteria.9 The diagnosis of asthma was established by typical symptoms and improvement in the prebronchodilator FEV1 of >15% after salbutamol inhalation (200 mcg). Their asthma was classified as...
mild-moderate according to National Asthma Education and Prevention Program (NAEPP) criteria based on FEV1 between 60 and 85% of predicted values, asthma symptoms that occurred once or more per week and two usages or more of as-needed bronchodilator per week [9]. Patients had not received corticosteroids or anti-leukotriene therapy prior to the study. The study took place from September 2003 to April 2004 when the exposure to dust was at a constant level and all children remained in the same environment.

**Ethics:**
All parents gave their written consent for participation in this study.

**Study design:**
This was a study comparing the effects of monotherapy with beclomethasone, 600 mcg/day, (Becotide, GlaxoSmithKlin) delivered by metered dose inhaler with spacer (Aerochamber, Monaghan Medical, Plattsburgh, NY), and montelukast sodium, 5 mg chewable tablets (Singulair, Merck & Co., Inc.) on serum levels of total IgE, clinical asthma score and FEV1. A placebo was not included because of ethical concerns. At the first visit we enrolled subjects and put them on beta 2-agonist, salbutamol, (Ventolin, Glaxo Wellcome, UK) ‘as needed’ for symptomatic relief purposes. They were informed of the aim of the study and were told how to score asthma symptoms and to use the inhaler with the spacer. At the second visit the subjects were randomized for treatment with:

1st group: beclomethasone 600 mg/day (300mcg twice daily) with montelukast placebo (30 patients);

2nd group: single dose of montelukast 5 mg/day at night, with beclomethasone placebo (30 patients).

The next visits were monthly for 6 months of treatment. Measurement of serum IgE and lung function testing in individual patients took place on the same day before starting treatment protocol and then after 3 months and 6 months. At each visit a short history was taken and the subject’s diary was evaluated. Salbutamol was withheld for at least 12 hours before lung function testing.

**Skin prick tests:**
Skin prick tests for common inhaled allergens (Pasteur, France) were performed to identify the presence of atopy. A mean weal diameter ≥3 mm and ≥ the histamine control was defined as a positive response. Skin prick tests were positive against D. pteronyssinus extract in all subjects participated in the study. None of enrolled subjects was allergic to seasonal allergens: pollens and molds.

**Diary card:**
The daily diary card included daytime symptoms (completed at bedtime by the parents) and incidents of nocturnal awakening (recorded in the morning upon awakening). The amount of as-needed beta 2-agonist was recorded daily as the number of puffs. Daytime asthma symptom score and nocturnal awakenings were scored subjectively, as follows: 0, no symptoms during the day/night; 1, symptoms but they do not affect any activities during the day/night sleep; 2, symptoms affect at least one daily activity/disturb night sleep; 3, symptoms affect two or more daily activities/disturb sleep all night or most of the night. Use of beta 2-agonists was scored: 0 = none, 1 = once a day, 2 = two to three times a day, 3 = more than three times a day. Minimum score for each day was 0 (no symptoms daytime, no symptoms at night and no use of beta 2-agonists). Maximum score was 9 (severe symptoms daytime and night and more than three uses of beta 2-agonists). Mean values were taken after each visit. The asthma questionnaire was based on the Pediatric Asthma Quality of Life Questionnaire and Scales previously shown to have acceptable evaluative measurement properties.18

**Laboratory tests:**
Three milliliters of blood were taken from each subject before starting treatment and after 3 months and 6 months of therapy. In each sample complete blood count (CBC) with absolute eosinophilic count was measured and also serum level of total IgE was measured using a commercially available immunoassay technique (Pharmacia CAP; Pharmacia Biotech, Uppsala, Sweden) according to the instructions of the manufacturer.

**Lung function measurements:**
FEV1 was measured by a spirometer (model PB 100/110, Puritan, Bennett, and Lenexa, Kans.). Children were encouraged to perform three successive maneuvers during each measurement. The largest FEV1 value from each set of measurements was used for analysis. Measures were taken as percent predicted values according to the recommendations of American Thoracic Society standards of acceptability and reproducibility.19

**Statistical Methods:**
The results were analyzed according to well-known statistical methods by using Stat Soft Statistical for Windows, release 6.0 (Stat Soft, Inc., USA). Student’s t test for paired data was used. P-values<0.05 were considered to be significant.

**Results:**
Fifty two subjects, 24 from the beclomethasone group and 28 from the montelukast group, completed the study. Four subjects were withdrawn from the study because of asthma exacerbation (need to inhale more
Table I: Patients baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Beclomethasone group(24)</th>
<th>Montelukast group(28)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>58</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.4±2.6</td>
<td>10.1±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1(%predicted)</td>
<td>76.5±1.5</td>
<td>77.2±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Total IgE (IU/ml)</td>
<td>363±66</td>
<td>358±54</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophilic count (cells/cmm)</td>
<td>542±71</td>
<td>580±60</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean and standard error of mean

Table II. Effects of treatment with inhaled corticosteroid or montelukast sodium on asthma symptoms score, FEV1 and total IgE level

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 months</th>
<th>3 months</th>
<th>6 months</th>
<th>P-level beclomethasone versus montelukast 6 months post treatment</th>
<th>P level pre-versus 3 months post treatment</th>
<th>P level pre-versus 6 months post treatment</th>
<th>P level 3 months versus 6 months post treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone group (24)</td>
<td>Score (points)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>FEV1 (%pred)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Total IgE (IU/ml)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic count (cells/cmm)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Montelukast group (28)</td>
<td>Score (points)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>FEV1 (%pred.)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>Total IgE (IU/ml)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>Eosinophilic count (cells/cmm)</td>
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<td>&lt;0.05</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tbody>
</table>

Values are expressed as means with standard error mean (SEM).

*Daytime, nocturnal asthma symptoms and use of b-agonists were scored as 0 (best) to 3 (worst) each

Fig. 1: Effect of treatment with inhaled beclomethasone and montelukast on asthma symptom score

Fig. 2: Effect of treatment with inhaled beclomethasone and montelukast on FEV1 in asthmatic children.

Fig. 3: Effect of treatment with inhaled beclomethasone and montelukast on total serum IgE level.
than six puffs of beta2-agonists per day) and others did not complete the study because of poor compliance with the inhaled medication. Characteristics of the subjects who completed the study are given in table I. Serum total IgE, total asthma scores and FEV1 measurements before and after treatment are presented in table II. At the beginning of the study, serum levels of total IgE, asthma scores and FEV1 did not differ among the beclomethasone and montelukast groups [table I]. Clinical scores and FEV1, significantly improved after 6 months of treatment (P<0.01 and P<0.05 respectively) with either inhaled beclomethasone or montelukast (figures 1, 2). Also, after 6 months of treatment, inhaled corticosteroid and montelukast significantly decreased the levels of blood eosinophils and serum total IgE (table II, figure 3). The effect of treatment with inhaled corticosteroid on total IgE did not differ significantly than the effect of Montelukast (table II). There were no significant differences between the beclomethasone and montelukast groups regarding the clinical parameters and FEV1 after treatment (table II). After 3 months all parameters improved significantly than pretreatment values (p <0.05). Also, after 6 months, serum IgE, asthma scores and FEV1 improved significantly than after 3 months values (table II).

**Discussion:**

Children with persistent asthma are in need of controller therapy. Currently, inhaled corticosteroids are recognized as the preferred long-term control therapy in patients with persistent asthma, including children of all ages. Leukotriene modifiers medications are alternative or additive controller medications in the treatment of patients with persistent asthma. Ideally, however, the decision to choose oral leukotriene modifiers in preference to an inhaled corticosteroid should be evidence-based. To date, there are few clinical trials compared the controller therapies in children. Since IgE is considered to play a crucial role in the allergic immune responses the reduction of free IgE levels is a rational target in the treatment of allergic diseases. We compared the effects of two controller medications, beclomethasone and montelukast, on serum IgE and clinical parameters in asthmatic children. The present study showed a significant decrease of serum levels of IgE after treatment with inhaled beclomethasone. Since there is no placebo group we cannot be sure to what extent the declines in IgE could relate to environmental effects but the fact that all children were not allergic to seasonal allergens suggest that the changes in IgE are most likely treatment related. These results compare favorably with those revealed by Ohru et al., where 3 months treatment with inhaled beclomethasone dipropionate (800 mcg/day) in adult asthmatics significantly decreased total serum IgE levels and specific IgE antibodies to house-dust mite and cedar. Also they found that the decreases in total serum IgE significantly correlated with an improvement in asthma symptom scores. Nong et al. examined children suffering from moderate to severe asthma who were treated with 100 mcg per day of fluibacine propionate or 200 mcg per day of beclomethasone dipropionate and noted no influence on serum IgE levels. This may be due to the relatively low dose of inhaled corticosteroids which cause no change in serum IgE. There are, also, some inconsistent data published in the 1970s regarding the effect of systemic administration of corticosteroids on IgE. Johansson suggested that systemic corticosteroids had no effect on the serum level of IgE whereas Kumar et al. reported that systemic administration of corticosteroids decreased serum IgE in atopic children. Recent evidence in a mouse model has shown that treatment with daily budesonide significantly lowered the total serum IgE level and was effective in decreasing lung inflammation, lowering eosinophil peroxidase activity and peripheral blood eosinophils in experimental asthma. Leukotriene receptor antagonists have recently been introduced as a novel asthma therapy with bronchodilatory and anti-inflammatory properties. Leukotriene modifiers medications prevent the effects of proinflammatory leukotrienes by either inhibition of enzymatic production of leukotrienes or by antagonism of leukotriene receptor binding. Tohda et al. showed in an in vitro study that panlukast, an anti-leukotriene agent, acts directly on peripheral blood mononuclear cells and can dose-dependently suppress the production of IL-4, IL-5 and GM-CSF in patients with bronchial asthma. There is only sparse information available on the effects of anti-leukotriene agents on serum levels of IgE in children. The findings of our results revealed that montelukast significantly reduced the serum total IgE after three and six months. Wu et al. determined the effect of a 3-day course of high-dose montelukast (25 mg/kg) on mediators of airway inflammation induced by a single allergen challenge in ovalbumin-sensitized mice. IL-4 levels in the lung and BAL, and IL-13 levels in the lung significantly decreased after treatment with montelukast. Serum IgE level was significantly lower in treated animals as well as significant reduction was found in IL-5 in the BAL, lung and the serum, and IL-5 mRNA expression in the lung. They suggest that montelukast inhibited the serum total IgE as a result of the reduction in IL-4.
suggested that a decreased percentage of CD11b CD4+ T cells might lead to down-regulation of IgE synthesis in their interaction with CD23- expressing B cells. Benda et al.\textsuperscript{30} showed that montelukast decrease IgE and Eosinophilic Cationic Protein and also improve bronchial hyperreactivity in children but its effect according patient selection. In our study the effects of montelukast on total serum IgE did not differ significantly than the effects of inhaled beclomethasone. The present study has shown significant improvement in clinical parameters—clinical score and FEV1—for treatment with beclomethasone as well as with montelukast in children with asthma. Surprisingly, no significant difference was found between both treated groups. Owen et al.\textsuperscript{31} showed that once-daily inhaled corticosteroid and leukotriene antagonist improved bronchial hyperresponsiveness and lung functions by a similar degree. Malmstrom et al.\textsuperscript{32} remarked that some patients experience large increases in FEV1 in response to treatment with beclomethasone or montelukast, whereas other patients experience small improvements. Riccionia et al.\textsuperscript{33} showed that administration of fluticasone and montelukast improved lung function and bronchial hyperresponsiveness. Hofstra et al.\textsuperscript{34} and Donahue et al.\textsuperscript{35} showed that corticosteroids are effective in increasing lung function, reducing bronchial hyperresponsiveness, preventing exacerbations and hospitalization in asthmatic children, and in reducing airway inflammation. Pizzichini et al.\textsuperscript{36} and Reiss et al.\textsuperscript{37} showed that montelukast improves asthmatic inflammation and prevents bronchoconstriction. Ahmet et al.\textsuperscript{38} concluded that treatment with inhaled corticosteroid budesonide is preferred, but leukotriene antagonists are alternative controller medications in mild persistent asthma.

**Conclusion:**

Inhaled beclomethasone or oral montelukast represents a therapy which improves IgE-mediated allergic inflammation, improve lung function and improve clinical parameters in asthmatic children. Although further studies are needed to compare other effects of montelukast and inhaled corticosteroids on asthmatic children and also since allergic factors play a role in more than 90% of cases of childhood asthma, our results are promising that single oral dose may replace inhaled medications and improve compliance with long term therapy in children with persistent asthma.

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**References:**

1. American Academy of Allergy, Asthma, and Immunology (www.aaaai.org).
14. Edelman JM, Milewski KA, Turpin JA, Santanello NC, Bird SR, Rader CR. Effectiveness and safety of montelukast, a leukotriene receptor antagonist, compared to inhaled cromollyn in moderate asthmatic


