Comparative efficacy of once-daily therapy with inhaled corticosteroid, leukotriene antagonist or sustained-release theophylline in patients with mild persistent asthma

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Summary The purpose of this study was to compare the efficacy and safety of the inhaled budesonide, sustained-release theophylline and montelukast, a leukotriene receptor antagonist, in patients with mild persistent asthma. In this single-center, randomized, parallel-group study that not designed blindly and placebo-controlled manner, 74 patients with mild persistent asthma were treated with either inhaled budesonide 400 μg once daily, oral montelukast 10 mg once daily, or sustained-release theophylline 400 mg once daily for 3 months.

In all three treatment groups, improvements were attained in overall asthma control. Asthma symptom scores and supplemental β2-agonist use were quite the same in all three treatment groups ($P > 0.05$). Although inhaled budesonide group resulted in significantly greater improvements compared with the other two groups in the lung functions ($P < 0.05$), the changes in FEV₁ and PEF are within the baseline variability and there was no statistically significant difference among the groups when analyzed by treatment month ($P > 0.05$). Exacerbations of asthma were experienced by 16% of the patients in the montekulast group, by 12.5% of the patients in the theophylline group, and by none of the patients in the budesonide group. The adverse event in each of the three groups was 12%, 16% and 16.7%, respectively.

It is concluded that the most important clinical parameters do not point that one of the treatments is more effective than others. Treatment with inhaled corticosteroid is preferred, but sustained-release theophylline and leukotriene antagonists are alternative controller medications in mild persistent asthma.

KEYWORDS
Asthma; Budesonide; Montelukast; Theophylline; Treatment

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Introduction

In order to take asthma under control and maintain, controller medications with anti-inflammatory properties are recommended as the primary long-term control medications in patients with mild persistent asthma. Because alternative controller medications, theophylline and leukotrienes, are less effective than inhaled glucocorticosteroid, treatment with an inhaled glucocorticosteroid is preferred in patients with mild persistent asthma according to the GINA 2002 Report. More clinical experience is necessary for being sure about alternative controller medications roles in the treatment of patients with mild persistent asthma.
Leukotriene modifiers medications prevent the effects of proinflammatory leukotrienes by either inhibition of enzymatic production of leukotrienes or by antagonism of leukotriene receptor binding.\textsuperscript{2} It is specified that theophylline, a bronchodilator medicine, has an anti-inflammatory effect which is due to an unknown mechanism at the low concentrations (5–10 mg l\textsuperscript{-1}).\textsuperscript{3–6} To date, because few clinical trials have compared the clinical efficacy and safety of control therapies, the benefits of these drugs within an asthma management program are not very clear. In patients with mild persistent asthma, studies that compare the efficacy of the other medications recommended as an alternative to inhaled corticosteroid treatment should be done. In addition, evidence is accumulating that once-daily treatment may be as effective as twice daily administration, although inhaled corticosteroids have traditionally been given twice daily.\textsuperscript{7,8}

For this reason, we designed a study to compare the efficacy of three different treatment given once-daily protocols in mild persistent asthma.

Patients and methods

Patients

A total of 74 patients, aged 23–45 years (mean 34.6±5 years), defined as having mild persistent asthma according to the criteria of Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention Program Report\textsuperscript{1} were enrolled in the study. The forced expiratory volume in one second (FEV\textsubscript{1}) at baseline had to be at least 80% of the predicted normal value, with an increase of at least 15% in FEV\textsubscript{1} from the baseline value after the inhalation of 400 μg of salbutamol. All of the patients were previously using inhaled budesonide at a dose of 200 μg a day or equivalent doses of beclomethasone dipropionate or fluticasone propionate and short-acting β\textsubscript{2}-agonist irregularly for at least 2 months prior to study. Patients were excluded if they had respiratory tract infection, smoked cigarettes or had a respiratory disorder other than asthma disease, had asthma exacerbations within the preceding 2 months, pregnant or lactating women or with hypersensitivity to sympathomimetic amines and women of childbearing potential who did not use a reliable contraceptive method. All of the patients gave their written informed consent, having been informed about the details of the study.

This clinical trial was a single-center, randomized, parallel-group study that not designed blindly and placebo-controlled manner. The study had a 3-week run-in period, followed by 3 months of randomized treatment. All patients entering the run-in period received inhaled budesonide at a dose of 200 μg twice daily, plus 250 μg of inhaled terbutaline as needed. After a run-in period of 3 weeks, eligible patients were randomized to each treatment group in simply random sampling method according to random numbers table. To these groups the following three different treatment combinations were applied:

- First group (n = 25): inhaled corticosteroid (Budesonide 400 μg once daily).
- Second group (n = 25): Leukotriene receptor antagonist (Montelukast 10 mg once daily).
- Third group (n = 24): Sustained-release theophylline (400 mg once daily).

Furthermore, all patients were given short-acting β\textsubscript{2}-agonist(terbutaline) inhaler as needed. Concurrent use of any medications that could interact with the drugs used in the groups was not allowed.

Assessments

Demographic characteristics were recorded at the start of the run-in period and patients were given a diary card to record symptoms, bronchodilator use and use of study drug. Day-time and night-time symptom scores were recorded separately.

The day-time asthma symptom score: 0 = no breathing problems at all, activity not restricted; 1 = breathing problems with little or no discomfort, and no activity restriction; 2 = breathing problems with some discomfort, and limitation of strenuous activity; 3 = breathing problems with discomfort and limitation of routine activity; 4 = breathing problems at rest with major discomfort and limitation in routine activity.

Night-time asthma symptom score: 0 = no breathing problems; 1 = one waking up because of breathing problems, but no use of rescue medication; 2 = one waking up because of breathing problems, controlled by rescue medication; 3 = more than one waking up because of breathing problems, controlled by rescue medication; 4 = difficult sleep because of breathing problems, despite use of rescue medication.\textsuperscript{9} PEF and the forced expiratory volume in 1 s (FEV\textsubscript{1}) were measured by spirometry during clinic visits at the start of drug treatment, and after 1, 2, 3 months of treatment before administration of study medications. The spirometer was calibrated before use by each new patient. The highest PEF value from three
satisfactory exhalations was recorded. In addition, during this control period, patients were assessed with respect to their harmony to the treatment, adverse events, keeping of daily cards in an orderly manner and the asthma exacerbations. Patients not obeying the study protocol and observing asthma exacerbations were withdrawn from the study. Asthma exacerbations occurring during this study were defined as any worsening of asthma symptoms requiring a change in the patient’s asthma therapy other than increased use of supplemental terbutaline.

This study was conducted in accordance with the Declaration of Helsinki amended the 52nd WMA General Assembly (Edinburgh, 2000), and approved by local ethics committees.

Statistical analysis

Data processing and statistical analysis were performed using GraphPad InStat (V2.04a). The primary objective of this study was to compare the effect of the three treatment regimens for the entire 3-month treatment period. The primary efficacy measure was morning PEF. Secondary efficacy measures included asthma symptom scores, supplemental terbutaline use, FEV₁ and asthma exacerbations. A sample size of 25 patients per treatment arm was estimated to provide greater than 80% power to detect a significant difference of 12 l min⁻¹ in morning PEF measurements at a significance level of 0.05. For all endpoints, the average response (change from baseline or percent change from baseline) was compared among treatments by using an analysis of variance (ANOVA) model. Tukey test was used to assess the groups which create significant difference. Symptom scores which was not normally distributed were analyzed using the Freidman test and Kruskal–Wallis test was used to compare the differences between the treatment groups. Mann–Whitney U and Wilcoxon tests by using Bonferroni correction were performed in order to analyze which groups have significantly different. All data were expressed as means ± standard deviation. P-value of less than 0.05 was accepted as statistically significant.

Results

A total of 74 patients (59 women and 15 men) were enrolled in the study. The demographic and baseline disease characteristics are similar in all three groups (Table 1).

### Lung functions

There was no statistically significant difference among the groups in the initial morning PEF values (P > 0.05, Table 1). Although inhaled budesonide group resulted in significantly greater improvements compared with the other two groups in morning PEF at the end of the treatment (P < 0.001, Table 2), the change in morning PEF was within the baseline variability and there was no statistically significant difference among the groups when analyzed by treatment month (P > 0.05, Table 2).

The baseline FEV₁ values were similar in all three groups (P > 0.05, Table 1). Although a significant change from baseline at endpoint for FEV₁ was seen in the budesonide group compared with the other groups (P < 0.05), no statistically significant difference was seen among the groups in the second and the third month of the treatment (P > 0.05, Table 2).

### Asthma symptom scores

No statistically significant difference was seen among the groups in the initial day-time symptom scores (P > 0.05, Table 2). A significant decrease in day-time symptom scores was noted in all groups after second month of treatment (P < 0.001). The decrease in symptom score continued during the third month of the treatment, but no statistically significant difference was observed among the groups (P > 0.05).

<table>
<thead>
<tr>
<th>Groups (n = 74)</th>
<th>Sex (F/M)</th>
<th>Age (yr)</th>
<th>FEV₁ (% pred.)</th>
<th>PEF morning (l/min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Group (n = 25)</td>
<td>20/5</td>
<td>35.9 ± 5</td>
<td>84.5 ± 4.1</td>
<td>368.4 ± 74.6</td>
</tr>
<tr>
<td>2 Group (n = 25)</td>
<td>21/4</td>
<td>34.3 ± 5</td>
<td>84.8 ± 5.3</td>
<td>371.2 ± 76.8</td>
</tr>
<tr>
<td>3 Group (n = 24)</td>
<td>18/6</td>
<td>33.5 ± 5</td>
<td>86.6 ± 5.5</td>
<td>378.9 ± 72.1</td>
</tr>
</tbody>
</table>

Data are presented as mean ± sd. M: male; F: female; FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow.
The initial night-time symptom scores of the patients were almost at the same level and there was no statistically significant difference among the groups (P > 0.05). While a significant decrease in the night-time symptom score was seen in the inhaled budesonide group in the first month of the treatment (P < 0.017), a significant decrease in the night-time symptom score was seen in the second month of the treatment in the montelukast and theophylline groups (P < 0.001). Nevertheless, no statistically significant difference was seen among the groups in the third month of the treatment (P > 0.05).

Supplemental $\beta_2$-agonist use

There was no statistically significant difference among the groups in the initial supplemental $\beta_2$-agonist use (P > 0.05, Table 2). A statistically significant decrease in supplemental $\beta_2$-agonist use was seen in all three groups after the first month of the treatment (P < 0.001) and the significant decrease continued in the second and third month of the treatment. There was no statistically significant difference among the three groups during the treatment period (P > 0.05).

Adverse events

Adverse events were reported by 12% of patients receiving inhaled budesonide treatment (dysphonia in one patient and cough in two patients), 16% of patients in the montelukast treatment group (headache in one patient, dyspeptic complaints in 3 patients) and 16.7% of patients in the theophylline treatment group (headache in one patient, dyspeptic complaints in 3 patients). One patient was withdrawn from the study due to serious dyspeptic complaints in the theophylline group.

Asthma exacerbations

Throughout the study, asthma exacerbations were experienced by 4 patients (16%) and 3 patients (12.5%) in the montelukast and theophylline treat-
ment groups, respectively. No asthma exacerbation was seen in the budesonide group.

Discussion

Inhaled corticosteroids have currently taken a leading role among the controller medications in current asthma guidelines for the management of patients with mild persistent asthma.\(^1\,\,{}^{10}\) However, it is a matter under discussion that the utility and placement of leukotriene antagonist and sustained-release theophylline for patients with mild persistent asthma. In this study, the efficacy and safety of inhaled budesonide, and leukotriene receptor antagonist and sustained-release theophylline accepted as alternative controller medications, were compared for the first time in patients with mild persistent asthma. Inhaled budesonide group resulted in significantly greater improvements compared with the other two groups in the lung functions (\(P<0.05\)). However, the changes in FEV\(_1\) and PEF are within the baseline variability and there was no statistically significant difference among the groups when analyzed by treatment month (\(P>0.05\)). Dahl et al. showed that theophylline made no significant increase in the FEV\(_1\) value throughout a treatment period of 9 months in asthmatic patients with an approximately 70% FEV\(_1\) values at the beginning, but they found that there was a significant increase in the inhaled budesonide groups compared with the pretreatment period. However, PEF values were unchanged during the study period in the inhaled budesonide and theophylline group.\(^{11}\) On the other hand, Busse et al. stated that there was a significant increase in morning PEF and FEV\(_1\) values of fluticasone propionate compared to montelukast in asthmatic patients with 50–80% FEV\(_1\) values at the beginning.\(^{12}\) In another study, montelukast had a significant increase in morning PEF and FEV\(_1\) values compared to placebo in patients with asthma with 40–80% FEV\(_1\) values in the initial state.\(^{13}\) However, no statistically significant increase in the FEV\(_1\) values was seen in our montelukast and theophylline groups compared to initial values. It may be related with the condition that FEV\(_1\) values of all patients were already over 80% at the beginning.

No statistically significant difference was seen in the symptom scores and supplemental \(\beta_2\)-agonist use among the three groups at the end of the treatment (\(P>0.05\)). GINA include leukotriene modifiers among the long-term control medications but the utility and placement of leukotriene antagonist within the therapeutic management of mild persistent asthma is unclear.\(^1\) In our study, montelukast treatment resulted in improvements in asthma symptom scores and decrease in supplemental \(\beta_2\)-agonist use, but asthma exacerbations were seen in four patients (16%). Dempsey and et al showed that leukotriene antagonist and once-daily treatment with low dose inhaled corticosteroid produced similar improvements, but only the inhaled corticosteroid suppressed exhaled nitric oxide, circulating eosinophils and ECP.\(^{14}\) Low dose fluticasone propionate was found more effective than montelukast as first-line therapy for patients with persistent asthma demonstrated FEV\(_1\) of 50–80% of the predicted normal value.\(^{12}\) Further clinical experience is necessary to establish their roles in mild persistent asthma.

Recent studies have shown that there is no difference between using low-dose inhaled corticosteroids plus theophylline and using only the high-dose inhaled corticosteroids.\(^{15}\) However, to our knowledge, there is no comparative data within mild persistent asthma therapy. No statistically significant difference was found at the end of the treatment between the theophylline group and the other two groups with respect to asthma symptom scores and supplemental \(\beta_2\)-agonist use. However, asthma exacerbations were seen in 3(12.5%) patients. Dahl et al. showed that long-term treatment with high dose of inhaled budesonide was superior to a low daily budesonide dose and oral theophylline in improvement of lung function, bronchial reactivity and asthma symptoms.\(^{11}\) Theophylline is a cheap and easily applied medicine. However, its side effects and the difficulty of monitoring the treatment make this medicine less preferred.

In our study, we compared the effect of three different treatment in steroid-pretreated asthmatics. For this reason, the impact of our study to answer the question about the effect of once-daily therapy with inhaled corticosteroid, theophylline and leukotriene antagonist in patients with mild persistent asthma is limited. However, our study may throw light on the studies about the first line therapy in naive patients with mild persistent asthma. The lack of placebo group is disadvantage of our study. Because no placebo group was examined in our study, it is not clear whether the clinical treatment effects are different from placebo.

Although inhaled corticosteroids have usually been given twice daily, previous studies are accumulating that once-daily treatment may be as effective as twice daily administration.\(^{7}\) Inhaled budesonide once-daily administrated resulted in improvements in lung function, symptom scores and supplemental \(\beta_2\)-agonist use and there
was no asthma exacerbation or serious side effects in any of our patients. The reversible esterification of budesonide provides a scientific rationale for the successful use of inhaled budesonide once-daily treatment. Altman et al have shown that administering 10, 50, 100 and 200 mg montelukast once- or twice-daily produced no clinical difference in accordance with the dose or once or twice daily administration. Once-daily treatment may be expected to offer advantages in terms of simplicity and convenience to the patient and enhanced compliance in the long-term control medications. Haataela et al. suggest that maintenance therapy can usually be given at a reduced dose in patients with mild asthma because discontinuation of treatment is often accompanied by exacerbation of the disease.

While no patients had asthma exacerbation or side serious effects of the drug in inhaled budesonide group during the study period, 4(16%) patients had asthma exacerbations in the montelukast group and 3(12.5%) patients had asthma exacerbations, and a patient had serious dyspeptic complaints in the theophylline group. Because an important goal of asthma therapy is the prevention of worsening asthma, asthma exacerbation rate is considered the most important indicator, although these agents improve overall control of asthma.

The disadvantage of our study was that the treatment was not designed blindly and placebo-controlled manner. Additional studies, particularly double-blind and double-dummy design, should be done for being sure about the clinical treatment effects. In our study, it is not clear whether the inhalative route itself may have a positive effect on subjective outcomes and compliance, because no dummies for the different treatments were used.

Improvements were attained in overall asthma control in all groups, as a result of treatments applied. The most important clinical parameters do not point that one of the treatments is more effective than others. Symptom scores, supplemental $\beta_2$-agonist use, and the percentage of adverse effects were quite the same in all three treatment groups. The only striking difference is the absence of exacerbations in the budesonide group in our study.

In conclusion, the results of this study show that treatment with inhaled corticosteroid is preferred, but sustained-release theophylline and leukotriene antagonists are alternative controller medications in mild persistent asthma. Because multiple daily administration of any therapy contributes to poor compliance, once-daily therapy enhanced compliance in the long-term control medications, especially asymptomatic or mild symptomatic patients. We believe that more clinical trials are necessary for being sure about the roles of leukotriene antagonists and sustained-release theophylline in the treatment program of mild persistent asthma.

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References


