Tapering Dose of Inhaled Budesonide in Subjects with Mild-to-Moderate Persistent Asthma Treated with Montelukast: A 16-Week Single-Blind Randomized Study

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Abstract. Pharmacological therapy with inhaled steroids (IS) is currently considered the gold-standard of treatment for mild-persistent asthma. Leukotriene receptor antagonist drugs (LTRAs) play an important role associated with IS, allowing dose tapering and maintaining control of asthma symptoms. The aim of this study was to determine the effectiveness of montelukast (MON) to allow tapering of the inhaled dose of budesonide (BUD) in patients with mild-moderate persistent asthma. This 16-wk single-blind randomized study included 40 asthmatic patients divided in 2 treatment groups. After a run-in period (4 wk), in which all patients inhaled 400 µg of BUD twice daily (bid), group A (20 patients) received MON (oral, 10 mg/day) combined with inhaled BUD (400 µg/bid), while group B (20 patients) was treated with BUD for the whole period of the study. In both groups, at every 4 wk the dose of BUD was halved. After 12 wk of treatment the mean value of forced expiratory volume during the first sec (FEV1, as % of predicted value) was significantly greater in group A compared with group B (94 ± 7.5 vs 83.1 ± 6.9; p<0.005). The mean values of peak expiratory flow (PEF), the percentages of asthmatic exacerbations, and the use of β2-short-acting agonist (SABA) were similar in the 2 groups at 4, 8, and 12 wk. In conclusion, in patients with mild-moderate persistent asthma, MON therapy is useful in tapering the dose of IS in order to reduce its side effects and to maintain the clinical stability of the disease. (received 23 December 2004; accepted 17 April 2005)

Keywords: montelukast, budesonide, asthma therapy, leukotrienes

Introduction

The recent GINA Guidelines establish that for long-term treatment of patients with mild-to-moderate persistent asthma (levels 2 and 3), inhaled corticosteroids (IC) represent the primary drugs, while leukotrienes receptor antagonists (LTRAs) are considered a therapeutic option to be associated with the steroid therapy [1]. This clinical approach appears rational for 2 main reasons: first, leukotrienes (LTs) play an important role in the inflammatory process of asthma and corticosteroids, administered by inhaled [2], oral [3], or iv routes [4], do not reduce the LTE4 levels; second, corticosteroids are well known for their effectiveness, but show dose-dependent side effects [5]. Moreover, some studies have shown that asthmatic patients often receive IC doses that are higher than necessary [6].

Investigations have shown that BUD is effective and well tolerated in patients with asthma of various severity levels [7,8]. The International Guidelines recommend an initial dose of inhaled BUD of 200-400 µg/day in mild persistent asthma and 400-1000 µg/day in moderate persistent asthma [1]. Studies have suggested that in some groups of patients low doses of BUD are more effective than high doses. If this is true, the dosage of BUD could be reduced to minimize potential side effects [8,9].

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0901-7370/05/0300-0285. $1.25. © 2005 by the Association of Clinical Scientists, Inc.
Montelukast (MON), a powerful specific receptor antagonist of cysteinyl leukotriene (Cys-LT), improves the control of asthma in adults [10,11] and children [12]. Moreover, it has a protective effect in exercise-induced bronchoconstriction [13], reduces the eosinophile count in the sputum [4], improves the quality of life [15] and is well tolerated in patients with mild-to-moderate persistent asthma when administered in association with IC [16]. It appears that the clinical benefit of this drug allows reduction of the inhaled dose of IC while maintaining control of asthmatic symptoms [17]. A recent study showed that, by adding MON to the asthma therapy, it is possible to decrease the mean dose of IC significantly at 12 wk of treatment. These results have been corroborated at 48 wk of treatment, demonstrating that patients do not develop tolerance to MON [18].

The present International Guidelines do not provide a clear statement about the effect of MON to reduce the inhaled IC dose. The aim of this study was to evaluate the effectiveness of MON in tapering the inhaled dose of BUD in patients with mild-to-moderate persistent asthma and to establish a standard scheme for BUD dose-reduction, while maintaining control of the disease.

Patients and Methods

Subjects. From September to December 2003, at the Pathophysiology Respiratory Center of the SS. Annunziata Hospital in Chieti, Italy, 45 non-smoking subjects, age >15 yr, were enrolled (25 males, 20 females) in this study. The patients were selected from among subjects who came to visit a pulmonologist for respiratory function tests or pharmacological reversibility testing. The patients all suffered from mild-to-moderate bronchial asthma according to the GINA guidelines (FEV1 between 60 and 85% of the predicted value, according to NIH criteria [1]), with a clinical history of dyspnea, wheezing, chest tightness, or cough for at least 4 mo, with reversible airway obstruction (defined as an increase of FEV1 or PEF >12% after salbutamol administration) at the time of the enrollment visit (V1) or during the 4 preceding mo, and/or stable therapy with inhaled BUD (400 µg twice a day) and short-acting β2-agonist (SABA) as needed.

Excluded from the study were patients with other acute or chronic pulmonary diseases documented in the medical history; patients hospitalized for asthma within 4 mo prior to enrollment; patients with history of serious diseases such as cardiac arrhythmias, unstable diabetes, neoplasms, psychiatric illnesses; patients with hepatic insufficiency, renal, or gastrointestinal diseases; patients with upper respiratory infections in the last 3 wk; patients that had received oral, iv, or im corticosteroids within 4 mo before enrolment; and patients who had received long-acting β2-agonists (LABA), alone or in combination with corticosteroids. This research protocol was approved by the institutional Ethics Commission and was conducted according to the norms of Good Clinical Practice endorsed by the European Community.

Study design. This 16-wk single-blind randomized study was conducted in a group of 40 asthmatic patients. After a 4-wk run-in period, during which all the patients continued to use BUD (400 µg bid), the patients were randomly assigned to 2 groups. Group A (20 patients) was treated with inhaled BUD (400 µg twice daily) and oral MON (10 mg/day); group B (20 patients) was treated only with inhaled BUD (400 µg bid). In both groups the dose of BUD was halved at regular intervals of 4, 8, and 12 wk. During the enrollment visit (V1), all patients underwent a complete clinical examination, respiratory function tests, and a reversibility test with salbutamol. Written informed consent was obtained from patients who participated in the study, including the respiratory function tests.

Clinical diary. A clinical diary was given to each patient for daily recording of the number of SABA inhalations, the use of asthma drugs other than prescribed in the study (including oral corticosteroids), and the presence of symptoms.

Peak flow meter. The patients were each given a peak flow meter for measurement of PEF at home. They were instructed to measure the PEF at least twice each day (morning and evening) and to record the values. The physicians responsible for the study instructed their respective patients to call him/her within 12 hr after experiencing any worsening of the asthma, if the use of SABA exceeded 6 inhalations/day for 2 consecutive days, or if the PEF dropped below the 60% of the personal maximum value established for each patient, so that the physicians could arrange for additional drugs, admission to the hospital, or a visit to the emergency room.

Programmed visits. Follow-up visits were scheduled at intervals of 4 wk (V2, V3, V4, V5). Each visit included examination of the clinical diary and the peak flow measurements, evaluation of treatment compliance, relief of possible drugs side effects, annotations of treatments and concomitant diseases, general objective examination, and spirometry. Following review of these data, the physician reduced the BUD dose in both treatment groups. The dose of BUD was halved according to the following scheme: BUD 800 µg/day in the period between V2 and V3, BUD 400 µg/day between V3 and V4, and BUD 200 µg/day between V4 and V5 (final visit).

Patient exclusions. Excluded from the study were patients with an incomplete diary; patients who had interrupted drug use for more than 5 consecutive days; patients who, according to the physician judgment, had failed to reduce the dose of the inhaled steroid; or patients who had shown worsening of the asthma and had begun systemic therapy with corticosteroids.
Drug tolerability. Drug tolerability profiles were evaluated by surveying the adverse events recorded in the clinical diary. Evaluation of adherence to the therapy was evaluated during each visit by checking the pill blisters and the returned empty inhalation devices.

Pulmonary function tests. Patients performed at least 3 forced vital capacity (FVC) manoeuvres according to the American Thoracic Society Standards [19]; the basal FEV1 and PEF values were the best among at least 3 significant tests. The bronchial reversibility test was performed (V1) by repeating the spirometric measurements 15 min after inhalation of 200 µg of salbutamol.

Statistical analyses. Statistical analyses were performed by the SPSS program, version 10.05 (SPSS, Inc., Chicago, IL, USA). Data were expressed as mean ± SD. The Student t-test was used for paired data. The frequency of asthmatic exacerbations and the use of SABA in the 2 groups were analyzed by the Chi-square test. Values of p <0.05 were considered statistically significant.

Primary end points were the mean values of FEV1 and PEF (expressed as % of the predicted value) measured during the visits (V1 to V5). Secondary end-points were the frequency of asthmatic exacerbations, the use of SABA, and the results of drug tolerability profiles.

Results

Baseline characteristics of the study population are shown in Table 1. Only 40 of 45 enrolled patients finished the study, of whom 20 were treated with BUD and MON (group A) and 20 treated only with BUD (group B). Five patients were excluded from the study: 2 patients (1 for each group) failed to show up for the first visit (V2) and were therefore excluded from follow-up. In 2 patients (1 from each group), it was not feasible to reduce the dose of BUD according to the prefixed scheme, owing to worsening of symptoms. One patient (group B) was excluded because of use of systemic corticosteroids for an asthmatic exacerbation.

The treatment groups were comparable in mean age (group A, 39.1 ± 14.5 yr; group B, 37.8 ± 13.2 yr); sex (group A, 9 men, 11 women; group B, 10 men, 10 women); basal FEV1 (group A, 91.0 ± 14.1; group B, 90.7 ± 10.4, as % of predicted value); and basal PEF (group A, 91.3 ± 9.7; group B, 89.7 ± 9.3, as % of predicted value) (Table 1).

Days with exacerbation of the asthma were defined as the appearance of one of the following: a reduction of the PEF >20% compared with the basal value, an increased use of SABA >70% compared with the basal value, or an attack of asthma (defined as worsening of the asthma that required a non-scheduled medical visit). After 12 treatment wk, when both groups consumed the smallest dose of BUD (200 µg/day), the mean value of FEV1 was significantly higher in group A compared to group B (94.0 ± 7.5 vs 83.1 ± 6.9; p <0.005, as % of predicted value).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% of predicted)</td>
<td>91.0±14.1</td>
<td>90.7±10.4</td>
</tr>
<tr>
<td>PEF (% of predicted)</td>
<td>91.3±9.7</td>
<td>89.7±9.3</td>
</tr>
</tbody>
</table>

* p <0.005 vs Group A
predicted value). However, the differences in mean values of PEF in the 2 groups at 4, 8, or 12 wk were not statistically significant (Table 2). The percentages of asthmatic exacerbations and the use of SABA were not significantly different in the 2 groups (Table 3). There was no meaningful difference between the 2 groups in the incidence of clinically adverse events (Table 4).

**Discussion**

This study indicates that the combination of MON and BUD in symptomatic patients with mild-to-moderate persistent asthma is useful to avoid the diminution of respiratory function indices during the tapering of the IC dose; this study also shows an additive effect of MON and IC. Patients treated with MON demonstrated improved FEV1 values compared to patients treated with only BUD (at the dose of 200 µg/day).

Such additive effects have been pointed out in studies that considered the bronchial reactivity tested with methacholine and assessed the patients' quality of life [20]. Our results agree with the data of other studies that have shown the positive effect of a combination of MON and IC on FEV1 and PEF [12,16,20,22]. Considering the damage that prolonged exposure to elevated doses of IC can induce, the therapeutic strategy employed in our study results in both functional and clinical control of the asthmatic disease; the strategy facilitates the use of the smallest doses of inhaled steroids, in agreement with the goals of recent international guidelines for treatment of asthma [1].

In the present study, the patients treated with MON had fewer asthmatic exacerbations and reduced use of SABA, although the differences between the 2 groups were statistically insignificant. The relatively small number of patients and the short treatment time (12 wk) may have been responsible for the lack of statistical significance. Therefore, a study with larger groups and longer follow-up is needed to evaluate these important facets.

In our study, MON therapy was well tolerated, which confirms the results of double-blind, placebo-controlled studies that have documented a good safety profile for MON in children and adults [10-13]. Good tolerability was also observed in the group treated with BUD, although the treatment period was relatively short considering the dosages of IC.

Our observation that most patients in the group treated with only BUD tolerated the reduction of the dose of IC, without significant worsening of the asthma, coincides with the data of studies that have shown that many asthmatic subjects receive doses of IC that are higher than necessary [6]. The short

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**Table 3. Asthmatic exacerbations (%) and SABA use (%) in the 2 treatment groups (secondary end points).**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Budesonide (800 µg/day)</td>
<td>Budesonide (800 µg/day)</td>
</tr>
<tr>
<td></td>
<td>Montelukast (10 mg/day)</td>
<td>Montelukast (10 mg/day)</td>
</tr>
<tr>
<td>Asthmatic exacerbations</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>SABA use a</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

a Short-acting β2-agonist use

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**Table 4. Adverse effects reported in the patients' personal daily diaries.**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
duration of the study (12 wk) did not allow us to estimate how many patients would remain clinically stable despite the reduction of the IC dose.

Our results show that MON can be useful in long-term treatment of asthmatic disease in association with relatively low doses of inhaled IC in subjects who would otherwise require higher doses of inhaled IC. Adding MON to IC, with a fixed reduction scheme of the BUD dose from 800 µg/day to 200 µg/day, facilitates the control of asthmatic disease in patients with mild-to-moderate persistent asthma.

References


