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Effect of Inhaled Corticosteroids on Bronchial Hyperresponsiveness in Patients with Mild Asthma

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SUMMARY **We studied the effect of inhaled budesonide on bronchial hyperresponsiveness (BHR) in twenty mild asthmatic patients. The study was conducted as a randomized, double-blind, placebo-controlled study. Before entering the study, the patients performed methacholine inhalation challenge (MIC) using a reservoir method to assess BHR. Then, they were randomly allocated to receive budesonide turbuhaler (200 μg/dose) or placebo turbuhaler two inhalations, twice daily for eight weeks. During the study, each patient recorded daily asthma score and daily number of puffs of β_2 agonist and they were assessed at weeks 4 and 8. At the end of the treatment, MIC was repeated again. Patients receiving budesonide showed a significant improvement in airway responsiveness compared with those receiving placebo ($p < 0.05$). They also showed a significant improvement in asthma severity score and a significant decrease in β_2 agonist bronchodilator use. This study also suggested that inhaled corticosteroids may be the primary treatment in patients, even with mild asthmatic and well-controlled symptoms.**

Bronchial hyperresponsiveness (BHR) is defined as a condition in which there is an increased tendency of airways to develop exaggerated bronchoconstriction response to many stimuli such as respiratory tract infection, cold air, cigarette smoke, chemical and pharmacological agents.[1] BHR is important in the pathogensis of bronchial asthma. It is a consequence of airway inflammation.[2] The role of airway inflammation is so well established that it is incorporated into the definition of the disease and is an important target of therapy.[3] The mechanisms of air way inflammation, in both IgE-dependent and IgE-independent mechanisms, involve the release of various inflammatory mediators and cytokines such as prostaglandin metabolites, interleukins, granulocyte-macrophage colony stimulating factor (GM-CSF), intercellular adhesion molecule-1 (ICAM-I) and vascular cell adhesion molecule-1 (VCAM-I).[4,5] The net result is the ·ruitment of inflammatory cells in , especially eosinophils.[6,7] y, products of these s, eosinophil major basic BP) and various cellular ese inflammatory mediators cause airway epithelial damage and shedding, goblet cell hyperplasia, basement membrane changes, vascular leakage, and smooth muscle contraction.[8,9] Inflammatory processes contribute to increased bronchial reactivity through a direct effect on smooth muscle, by increasing airway wall thickness or via activation of the axon reflex.[10,11] Such inflammation has been found to exist even in patients with mild disease.[12] In a previous study, we found that Thai patients with mild asthma still had BHR to methacholine challenge at a mean concentration of 4 mg/ml.[13] Corticosteroids have to be effective in treatment of asthma by suppression of the inflammatory response, resulting in improvement of BHR.[14] Budesonide, an inhaled corticosteroid, has been used for many years in treatment of asthma.[15] Several studies have found that budesonide was effective in both short-term and long-term treat-

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ment of asthma and reduction of BHR.[16-18] In those studies, budesonide administered by a pressurised, metered-dose inhaler (MDI) with a spacer was used. At present there are several delivery systems using inhaler devices.[19] Budesonide turbuhaler, another type of delivery system, is claimed to be better than MDI because it has no propellent and it achieves greater drug deposition in the lung. Since there was no such study in Thailand, we investigated the effect of budesonide turbuhaler in Thai subjects.

The purpose of this study was to investigate the change of BHR in patients with mild asthma after 8 weeks of treatment with inhaled budesonide turbuhaler using the methacholine inhalation challenge (MIC) method.

PATIENTS AND METHODS

Subjects

Twenty subjects with mild bronchial asthma were enrolled in the study. They were selected from out-patients of the Chest and Allergy Clinic, Chulalongkorn Hospital. They were diagnosed as having bronchial asthma with the presence of coughing or wheezing in the past three years; their baseline spirometry showed a decrease of FEV_1/FVC of less than 70%, with an improvement in FEV_1 greater than 15% after inhalation of bronchodilator. All patients had been followed up in the clinics for many years. They were classified as having mild asthma, according to National Institutes of Health (NIH) guidelines,[20] which defined this condition as having few clinical symptoms (exacerbation of cough and wheezing no more than 1-2 times/week, nocturnal attack no more than 1-2 times/month) and minimal or no evidence of airway obstruction on spirometry. Most of the patients used long-acting theophylline once or twice daily, and inhaled a β_2 agonist bronchodilator as needed. None used systemic corticosteroids, ketotifen or disodium chromoglycate within the three months before entering the study.

At the time of study entry, MIC was performed. Then each patient was randomly allocated to receive budesonide turbuhaler 200 μg/ dose or placebo turbuhaler, 2 inhalations twice daily for 8 weeks. Each patient was given a diary card to record: (a) symptom scores with scale 0-3 (0 = no symptoms, 1 = mild symptoms easily tolerated, 2 = moderate symptoms causing interference with daily activity, and 3 = severe symptoms causing inability to work), (b) daily numbers of puffs of β_2 agonist MDI taken.

Patients came for check up at weeks 4 and 8. At the 8th week, MIC was repeated again by the same method.

Procedure

MIC was performed at 09.00 by using the procedure as previously described.[13] Briefly, stock solutions of methacholine in a citrate buffer were prepared under sterile conditions for each concentration; 0 (diluent), 0.5, 1, 5, 10, and 25 mg/ml. Six milliliters of the solution were filled in an atomized nebulizer part of the equipment (Provocation test I, Pari-Starnberg, Germany). It has been determined that about 0.4 ml of the solution is necessary to produce 10 litres of methacholine aerosol to fill the reservoir bag.

Before methacholine inhalation, baseline spirometry was performed with subjects standing using the Autospiror Discom-21 (Chest Corporation, Tokyo, Japan). At least three satisfactory and two reproducible spirometric maneuvers were required according to ATS recommendation.[21] The largest FEV_1 value from acceptable maneuver was used for the baseline FEV_1. Then each subject inhaled diluent aerosol from the reservoir bag via slow inspiratory vital capacity maneuver until the bag was empty. Three minutes after the inhalation, spirometry was repeated. The largest FEV_1 from an acceptable maneuver was used as the post-diluent control value. After that, subjects inhaled an increasing concentration of the methacholine aerosol (0.5, 1, 5, 10, and 25 mg/ml, respectively) from the reservoir bag. Spirometry was performed in a similar manner after inhalation of each concentration of methacholine, the largest FEV_1 from an acceptable maneuver being selected for analysis. The test was terminated if there was more than 20% decline from the control value of FEV_1 after any inhalation. At the end of the test, the subjects who had a decline of FEV_1 more than 15% was given one nebule of fenoterol and ipratropium bromide solution via nebulizer and spirometry was repeated 10 minutes later. Subjects were informed about the possible late phase reaction which could occur 6-8 hours after the test and they were discharged from the unit after their FEV_1 had returned to within 10% of their baseline values.

Data analysis

Subjects were categorized as having BHR (positive test) if they showed more than 20% decrease in FEV_1 (PC_{20}) from baseline after inhalation of diluent or any concentration of methacholine up to and including 25 mg/ml.[22]

Data were analyzed by computer using Excel 5.0. Results were presented as the mean ± standard deviation (SD). For comparisons of the mean value, the *t*-test was used. A p value of less than 0.05 was considered statistically significant.

RESULTS

The results of the study are presented in Table 1 and Figs. and 3. The mean values ± deviation for age, sex, h %FVC, FEV_1, %FEV_1 the first PC_{20} were not

Table 1. Subject characteristics in the study.

	Budesonide	Placebo	p-value
Age (years)	33.2±7.46	32.8±8.6	NS
Sex (F/M)	5/5	5/5	NS
Height (cm)	163.2±8.89	164.5±8.84	NS
FVC (l)	3.32±0.74	3.30±0.8	NS
% $FVC/FVC_{predicted}$	92.8±12.3	93.9±12.4	NS
FEV_1 (l)	2.79±0.65	2.76±0.75	NS
% FEV_1/FVC	85.1±8.89	84±7.89	NS
1st PC_{20} (mg/ml)	4.06±0.5	4.13±0.6	NS
2nd PC_{20} (mg/ml)	6.68±1.2	4.15±0.8	<0.05

different between the two groups. No patient withdrew during the study.

Although these patients had mild symptoms and were well-controlled at the time of enrollment, the patients who used budesonide still showed a significant improvement in asthma severity by asthma score, compared with those receiving placebo ($p < 0.05$) as shown in Fig. 1. None of these patients had acute exacerbation during the study. There was also significant reduction in the amount of inhaled bronchodi-

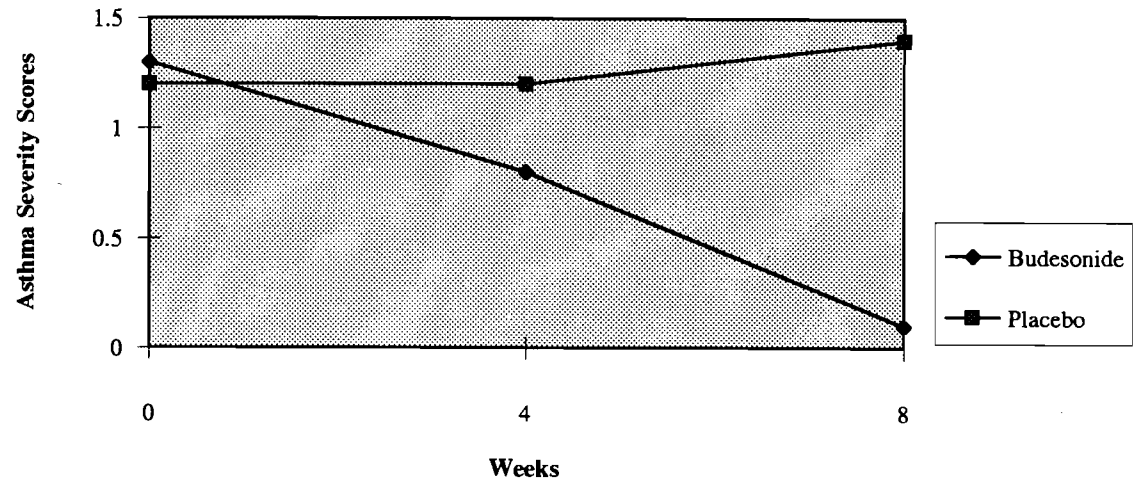

Fig. 1. Effect of budesonide on asthma severity scores.

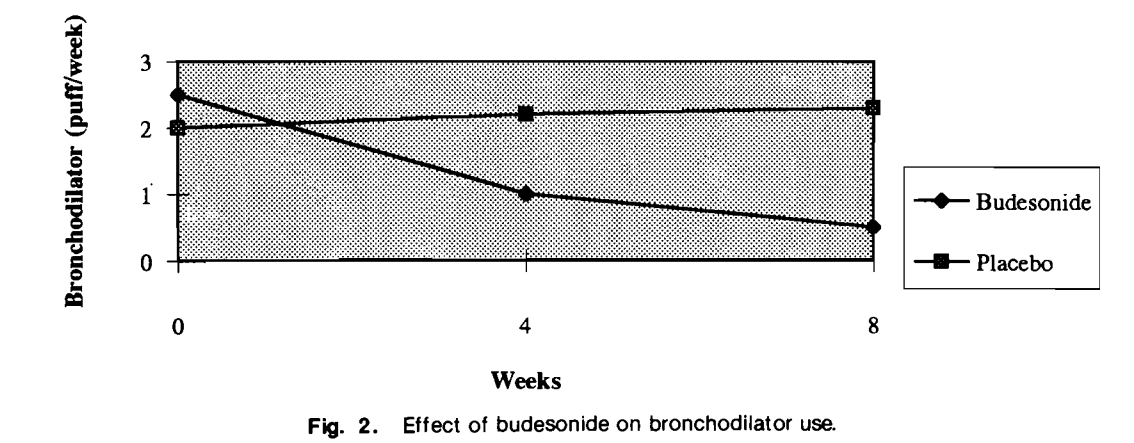

Fig. 2. Effect of budesonide on bronchodilator use.

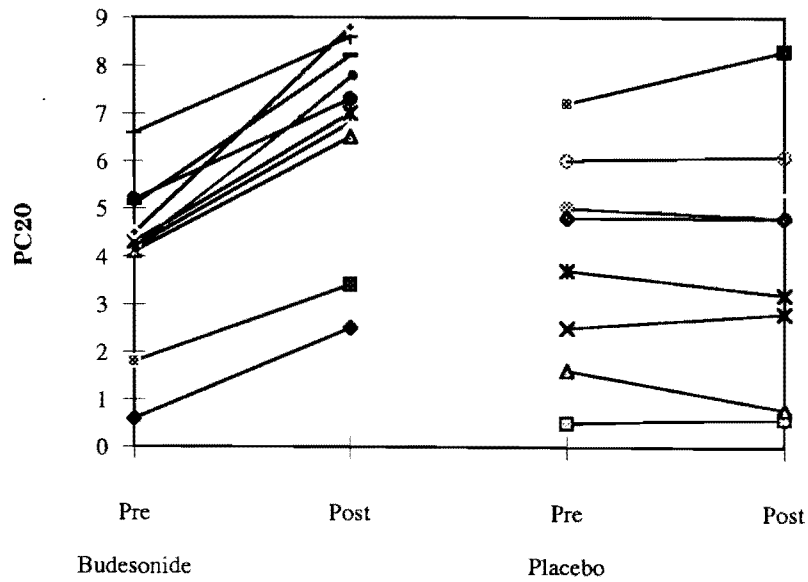

Fig. 3. Airway responsiveness to methacholine.

lators used by the budesonide group compared with those receiving placebo ($p < 0.05$) as seen in Fig. 2.

Patients receiving budesonide had an increase of PC_{20} corresponding to 0.6 doubling concentration of methacholine from the baseline to the end of treatment. In the placebo group, the increase was 0.004 doubling concentration which was significantly different from the budesonide group ($p < 0.05$) as shown in Fig. 3.

DISCUSSION

The mechanism of action of corticosteroids in asthma is related to their anti-inflammatory effects. They interfere with arachidonic acid metabolism and the synthesis of leukotrienes and prostaglandins, reduce microvascular leakage, inhibit cytokine production and secretion, prevent directed migration and activation of inflammatory cells, and increase responsiveness of beta receptors of the airway smooth muscle. Corticosteroids have shown to reduce epithelial damage and improve cellular morphology, reduce vascular leakage, reduce the numbers and activation of inflammatory cells, and inhibit the release of preformed and newly formed mediators from inflammatory cells which are related to the improvement in signs and symptoms of asthma as well as the improvement of BHR.[23-25]

The improvement of BHR by corticosteroids depended on dose and duration of the treatment. Kraan *et al.*[16] found an increase in PD_{20} to histamine of +0.4 doubling-dose (DD) after 2 weeks of treatment with 100 μg budesonide MDI twice daily, and a further increase to +0.8 DD after 8 weeks. Vethenen *et al.*[26] studied inhaled budesonide MDI 800 μg twice a day for 6 weeks in 40 asthmatic patients. They found that there was a significant increase in PD_{20} to +2.4 DD of histamine.

Juniper *et al.*[17] evaluated the effect of longterm treatment with inhaled budesonide MDI 400 μg daily for 1 year on BHR in 32 stable adult asthma. The patients receiving budesonide showed a fourfold mean improvement in BHR. The largest improvement occurred during the first 3 months. The improvement in BHR was also accompanied by significant improvement in asthma symptoms, the need for bronchodilator use and the number of asthmatic exacerbation. They concluded that regular and prolonged use of inhaled corticosteroid could produce marked improvement in BHR, sometimes with full resolution and clinical improvement. Moreover, they also demonstrated that, when inhaled corticosteroids were reduced after prolonged treatment, improvements in BHR could be maintained for at least 3 months before deterioration in symptoms, spirometry and increased airway responsiveness again.[27]

Kivity *et al.*[28] used budesonide MDI 400 μg twice daily for 8 weeks in 20 patients with mild to moderate asthma. They found that the treatment caused a moderate increase in spirometry which was significantly different from the placebo group. The BHR was also increased 1.8 DD but it was not statistically significant different when compared with the 0.8 DD of the placebo group.

Our study showed that mild asthmatic patients receiving inhaled budesonide turbuhaler 400 μg twice daily delivered a significant decrease in β2 agonist bronchodilator use with significant symptom control. In fact, even though these patients had been considered to be in good control initially, it appeared that there was still further clinical improvement when they regularly used inhaled budesonide turbuhaler. Although the improvement in the second PC_{20} in the budesonide group was only +0.6 doubling concentration, it was statistically increased when compared with the +0.004 of the placebo group ($p < 0.05$).

We do not understand the reasons why the improvement of

BHR in our study was so small when compared with those reports in the literature. It may be a technical error in turbuhaler usage resulting in lesser amount of drug deposition in the lower airway or it may be that budesonide turbuhaler was not as effective as budesonide MDI. In a further study we would compare the effectiveness of the turbuhaler and the MDI.

In conclusion, our study demonstrated that mild asthmatic patients receiving inhaled budesonide turbuhaler showed a significant improvement in asthma severity, decreased β_2 agonist use and reduced BHR, compared with those receiving placebo. However, the improvement of BHR was not so much, this needs to be clarified in a further study.

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