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Fluticasone Propionate and Bronchial Hyperresponsiveness in Childhood Asthma

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SUMMARY **Bronchial asthma is now agreed as being a chronic inflammatory disease of the airways. Inhaled steroids are widely accepted as a preventive medication in asthmatic patients of all ages and severity. However, the optimal use of inhaled steroids and the important issue of safety and efficacy still remain of concern, particularly in children. Recently, fluticasone propionate (FP) has been developed for use as an inhaled preparation for the treatment of asthma. Because of its high topical potency and increased lipophilicity, it is claimed that FP has an improved risk/benefit compared with other inhaled steroids. In order to evaluate the use of FP in children, we have studied the efficacy of high dose FP (500 μg/day) in asthmatic children. Thirteen children (9 boys and 4 girls), aged 7-17 years (10.8 ± 2.6), were instructed to use a pressurized metered-dose inhaler connected to a Volumetric® spacer. The standard methacholine bronchial challenge test was used as a principal outcome parameter. The PD_{20}, a cumulative dose of methacholine inducing a 20% decrease in FEV_1, was measured pre- and post-treatment with inhaled FP. After 4 weeks of FP, PD_{20} significantly increased from 21.6 ± 14.3 inhalation unit to 106.6 ± 78.5 inhalation unit (4.9 fold, $p = 0.004$) reflecting the improvement of airway reactivity. All subjects improved clinically. These results demonstrate that the anti-inflammatory action of FP 500 μg a day for four weeks can markedly reduce bronchial hyperresponsiveness, the basic physiologic abnormality in bronchial asthma.**

The recognition that airway inflammation is present even in the mildest of asthmatic patients[1] has led to the introduction of inhaled steroids at a much earlier stage in therapy.[2,3] There have recently been many important developments in understanding the efficacy of inhaled steroids in asthma therapy.[4] Furthermore, issues such as compliance, convenience, safety, and acceptability need to be considered when treating patients.

Fluticasone propionate (FP) is a trifluorinated glucocorticoid which has been developed for use as an inhaled preparation for the treatment of asthma.[5-8] Inhaled FP has been available in Thailand since 1996. FP has chemical modifications which decrease mineralocorticoid activity and increase potency and lipophilicity.[9] The highly lipophilic characteristic of FP plays a major role in dictating the pharmacological profile of the drug. The potential advantages of increase lipophilicity are: 1) increase uptake, penetration and deposition in lung tissue; 2) consequent slow release from the lung lipid compartment; 3) increased affinity for the glucocorticoid receptor; and 4) prolonged glucocorticoid receptor occupancy. These differences in biological properties appear to be predictive of clinical effects. Studies evaluating a variety of clinical outcome

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measures suggest that FP has a dose-dependent clinical potency that is at least twice that of beclomethasone dipropionate[10,11] and budesonide.[12-14] Another study compared the effect of two doses of FP Diskhaler (50 μg/d and 100 μg/d) with that of placebo among 166 asthmatic children.[15] Both FP doses significantly improved the clinical asthma symptoms. Interestingly, there was no significant difference between the effects of the two doses of FP in symptom scores and PEF. It has been suggested that the evaluation of clinical outcomes may not be sensitive enough to differentiate the effects of the doses of steroid. Therefore, more information with other outcome parameters such as airway hyperreactivity is needed to explore whether bronchial hyperresponsiveness can be a better outcome measure to distinguish the difference.

The purpose of this study was to evaluate the effect of inhaled FP therapy on airway responsiveness after bronchoprovocative challenge with methacholine in children with chronic asthma. We found that bronchial hyperresponsiveness was significantly reduced after a 4-week treatment with inhaled FP, whereas analysis of FEV_1 showed no significant difference between pre- and post therapy.

MATERIALS AND METHODS

Thirteen asthmatic children (nine boys, four girls) participated in the study. Mean age was 10.8 (range 7 to 17 years). All subjects had the clinical syndrome of paroxysmal cough, wheezing, and dyspnea which met the American Thoracic Society criteria for the diagnosis of asthma.[16] These children had a history of chronic asthma from the range of 1 to 11 years. In each individual, the initial FEV_1 before entering the study was at least 70% or higher (Table 1). At the time of the study, symptoms were controlled with inhaled β_2-agonist bronchodilators. None had used systemic steroids, inhaled steroids, ketotifen, or disodium cromoglycate in the previous month. Signed consent was obtained from the patients or parents.

Study Design

All patients were treated with inhaled FP 500 μg/day (2 puffs containing 125 μg twice daily) for 1 month. The major treatment outcome was the reduced airway reactivity as defined by PD_{20}. An additional asthma outcome measure included the compliance of the patients, which was assessed by interviewing, daily recording of symptoms as well as medication usage, and weighing the canisters. Approximately one canister containing 120 doses of FP had to be used in one month. The inhalation techniques were instructed to each patient using a pressurized metered-dose inhaler (pMDI) connected to a large volume spacer (Volumetric®). Mouth washing after taking medication was emphasized to reduce local and systemic side effects. Physical examination, FEV_1, and methacholine bronchial provocation test were assessed and recorded at the beginning and at the end of the study.

Methacholine challenge

The degree of airway hyperreactivity was assessed by methacholine inhalation test according to the method described by Chai *et al.*[17] The aerosols were generated by the deVilbiss Model 646 (DeVilbiss Co., Somerset, PA, USA) nebulizer attached to the Rosenthal Dosimeter (Sensor Medics Corp., Yorba Linda, CA, USA). The aerosols were passed into a mouthpiece and were inhaled by 5 deep inhalations. Isotonic nor-

Table 1 Patient clinical data

Patient No.	Age (year)	Sex	FEV_1 (% predicted)	Methacholine PC_{20} (mg/ml)
1	7	M	108	5
2	8	M	83	5
3	9	M	82	2.5
4	9	M	101	5
5	10	M	92	2.5
6	10	M	83	2.5
7	10	M	91	10
8	12	M	71	5
9	13	M	74	5
10	8	F	83	5
11	10	F	94	5
12	14	F	98	2.5
13	17	F	75	5
Mean ± SD	10.8 ± 2.6		87.3 ± 10.7	4.6 ± 1.9

mal saline was inhaled first and the largest FEV_1 was recorded as a baseline FEV_1 value. Then the patient was instructed to inhale the increasing concentration of methacholine in a dilution of 2.5, 5, 12.5, and 25 mg/ml at 5-minute intervals, respectively. After each dose of inhalation, FEV_1 was measured. The response was determined by the change in FEV_1 from the baseline. The test was terminated if there was more than 20% decline from the baseline FEV_1 value after any inhalation. The degree of airway reactivity was calculated into PD_{20} IU (Inhalation Unit), a cumulative dose of methacholine inducing a 20% decrease in FEV_1. Measurement of spirometry and PD_{20} for pre- and post-treatment were compared with student's paired *t*-test. Data are expressed as mean ± SD and a probability of < 0.05 was taken as significant.

RESULTS

Eleven out of thirteen patients demonstrated a marked decrease in bronchial hyperresponsiveness at the end of the study. Two patients showed no improvement in PD_{20} after the treatment. Of all patients, baseline mean methacholine PD_{20} was 21.6 ± 14.3 before inhaled FP, while the mean methacholine PD_{20} after a one-month treatment was 106.6 ± 78.5 (Table 2). The results demonstrated that one-month of 500 μg/day of inhaled FP induced significantly increased methacholine PD_{20} ($p = 0.004$). This reflected a 4.9 fold increase in PD_{20}.

There was no difference in FEV_1 mean values between before and after treatment (Table 3). During treatment, nine patients became symptom free. Four of 13 patients reported fewer symptoms of cough and chest tightness, which responded promptly with inhaled bronchodilators. One of the partial-responder subjects (patient #6) had one episode of upper respiratory tract infection during the third week of treatment, which may explain the poor response to inhaled steroid. All patients were satisfied with the medication. No side effect was observed during the study period.

Table 2 Response to methacholine challenge before and after the treatment with fluticasone propionate 500 μg/day for 4 weeks

Patient No.	PD_{20} (inhalation unit)	
	Pre-treatment	Post-treatment
1	19.9	144.6
2	35.5	199.6
3	4.4	19.8
4	38.9	151.0
5	7.0	12.0
6	5.8	4.9
7	49.1	34.7
8	21.6	73.3
9	38.9	180.2
10	14.1	59.8
11	16.9	188.0
12	9.9	91.9
13	18.7	226.0
Mean ± SD	21.6 ± 14.3	106.6 ± 78.5

Table 3 FEV_1 values before and after the treatment with fluticasone propionate 500 μg/day for 4 weeks.

Patient No.	FEV_1 (% predicted)	
	Pre-treatment	Post-treatment
1	108	97
2	83	89
3	82	90
4	101	99
5	92	93
6	83	81
7	91	85
8	71	81
9	74	82
10	83	79
11	94	93
12	98	93
13	75	73
Mean ± SD	87.3 ± 10.7	87.3 ± 7.5

DISCUSSION

We found a one-month treatment with FP effectively attenuated bronchial hyperresponsiveness in asthmatic children. At the conclusion of the study, there was an almost 5-fold decrease in airway hyperreactivity as assessed by methacholine bronchial challenge test (PD_{20}). In contrast, the assessment of FEV_1 showed no significant difference. These results confirm the concept that spirometry may not be a sensitive parameter to differentiate the efficacy of treatment in asthma.[4] Bronchial hyperreactivity is an important feature of asthma.[18, 19] A standardized methacholine bronchial provocation test provides information about the severity of the disease.[20] After prolonged treatment with inhaled steroid, a reduction in bronchial hyperreactivity is most likely due to a decrease in the inflammatory process.[21-23] The response depends on the dosage and duration of treatment. This study suggested that a daily dose of 500 μg FP resulted in significant improvement of bronchial hyperresponsiveness in asthmatic patients. FP was well tolerated as indicated by patient satisfaction and good compliance. There were no severe exacerbations during the treatment. Some patients were able to engage in more physical activities and could sleep more soundly. In addition, no abnormal findings were noticed on physical examination. However, to assess safety, further studies are required to establish other possible systemic side effects such as hypothalamic-pituitary-adrenal axis suppression, growth retardation and osteoporosis.

Several national and international guidelines have recommended the use of inhaled steroid as first-line prophylactic therapy in chronic asthma.[24, 25] By using questionnaires, we recently found that 70% of the pediatricians in Thailand prescribed inhaled steroid for their asthmatic patients [unpublished data]. Because of the variety of inhaled steroid formulations, it is important that good information regarding the efficacy and safety of these preparations should be available, particularly for the newer medications. To achieve the goals of asthma management (such as abolition of symptoms) it may be necessary that some patients will require higher doses of steroid than are currently given. However, the potential hazards from extended use of inhaled steroid need to be monitored.

In conclusion, we have found a 5-fold reduction in methacholine bronchial hyperresponsiveness in asthmatic children, who have been treated by a daily dose of 500 μg FP for 4 weeks. However, no changes in FEV_1 before and after therapy were noted. In addition, the medication was well tolerated without major side effects. It is important that asthmatic patients be prescribed the optimal dose of inhaled steroids to control their bronchial hyperresponsiveness and to reduce their symptoms.

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