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Original Article

Evaluation of factors that allow the clinician to taper inhaled corticosteroids in childhood asthma

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Abstract

Inhaled corticosteroids are potent and effective treatment agents for controlling symptoms of childhood asthma. However, there are no predictive factors that help to determine which patients with asthma are likely to be tapered off inhaled corticosteroids successfully. We examined whether any factor or combination of factors could help the clinician safely discontinue inhaled steroid therapy. Thirty-six asthmatic children whose symptoms were stable on low-dose beclomethasone dipropionate (BDP) were divided by parental choice into two groups: maintenance BDP (n = 11) and no BDP (n = 25). Methacholine inhalation tests were performed at the beginning of the study and after 1 month. Twelve children (48%) who had BDP discontinued developed exacerbations after 2–3 months, whereas there were no problems in the maintenance group. The no BDP group was retrospectively divided into two subgroups: exacerbation (+) and (–). The threshold to methacholine in the exacerbation (+) subgroup decreased significantly in advance of clinical symptoms. The two subgroups were analyzed statistically by two-group discriminant function analysis. The change in threshold to methacholine, the dose and potency of drugs, duration of asthma and gender (female) correlated with exacerbation. These results suggest that discontinuation of inhaled steroids should be done carefully, even in stable asthmatic children. The methacholine inhalation test, gender, drugs and history may be used as references for discontinuing inhaled steroids.

Key words: beclomethasone dipropionate, bronchial asthma, bronchial sensitivity, children.

Introduction

Bronchial hypersensitivity in asthma can be assessed by inhalation testing with bronchoconstricting agents, such as methacholine.[1] The degree of response to bronchoconstricting agents correlates well with the severity of the disease.[2,3] Recent studies have suggested that chronic bronchial inflammation, characterized by preferential infiltration of eosinophils, is an important factor in the development of hypersensitivity.[4,5] Inhaled corticosteroids are known to reduce bronchial sensitivity and are now widely used in asthma therapy.[6,7] However, evaluating long-term use of inhaled corticosteroids, such as beclomethasone dipropionate (BDP), is controversial because of the possibility of adverse events such as growth retardation. Although BDP at 800 μg/day or less is generally accepted to be clinically safe,[8,9] 200–800 μg/day may affect the adrenal function of children.[10] Furthermore, inhaled corticosteroids sometimes induce oropharyngeal candidiasis, skin atrophy[11] and glaucoma.[12] Thus, the clinician should maintain the lowest effective level of inhaled corticosteroids. It is important to emphasize the step-down in inhaled steroids during asthma therapy as

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well as step-up in steroids.[13] Bronchial sensitivity has been reported to increase within 1 week to 3 months after cessation or reduction of inhaled corticosteroid therapy.[14–18] We have attempted to describe factors to help the clinician safely discontinue inhaled corticosteroids.

METHODS

Subjects

Thirty-six asthmatic children (24 males and 12 females; age range, 8–19 years; mean, 12 years) treated at the out-patient clinic of Department of Allergy, National Children's Hospital were enrolled in this study with patients' and/or parents' informed consent about consecutive examination. The study was carried out from May 1996 to December 1996. All children were positive for IgE antibody for *Dermatophagoides farinae* (CAP system; Pharmacia, Uppsala, Sweden). They had been treated with low-dose inhaled BDP (100–200 μg/day) and were stable for at least 6 months (ratio of forced expiratory volume in 1 second ($FEV_{1.0\%}$) > 70%). Other clinical features and initial examination data for these patients are shown in Table 1. Subjects had received no oral or parenteral corticosteroid therapy during the preceding year. Parents were instructed to control allergens in the home environment. Instructions included using pillows consisting of only small fragmented plastic tubes, vacuuming floors, carpets and quilts once a week or more with a powerful (> 300 W) vacuum cleaner and avoiding stuffed dolls and furry pets.

Study design

This study consisted of two parts. Initially, we examined the effect of discontinuing BDP. Several laboratory tests, such as the methacholine inhalation test, were performed on all patients at the beginning of the study and 1 month after the cessation of BDP. Then we assessed which factors contributed to the exacerbation of asthma among those who discontinued BDP.

Table 1 Therapeutic score

Drugs	Method	Score
Steroid	Inhaler	1.0/each puff (50 μg)
β_2-stimulant	Internal use	0.5/each time
	Inhaler	0.5/each puff
Theophylline	Internal use	2.0/each time
Anti-allergic drug	Inhaler	1.0/each time (solution, powder)
		0.5/each puff (aerosol)
	Internal use	1.0/each time
Immunotherapy	Injection	4.0/each time

Therapeutic score as defined by the Japanese Society of Pediatric Allergy and Clinical Immunology. The score was calculated as a sum for all anti-asthma drugs used in 1 month.

We divided subjects who were stable for at least 6 months into two groups: the maintenance BDP group, whose parents wished to continue BDP ($n = 11$), and the no BDP group, whose parents wished to discontinue BDP ($n = 25$). The no BDP group was retrospectively divided into two subgroups: an exacerbation (+) group, whose condition worsened after discontinuation, and an exacerbation (–) group, whose condition remained stable. Several laboratory tests, including the methacholine inhalation test, pulmonary function test and measurement of blood eosinophil count and serum eosinophil cationic protein (ECP), were performed at the beginning of the study and 1 month after cessation of BDP. Both groups were evaluated clinically for 3 months.

We evaluated the following 11 factors for their correlation with worsening asthma: gender, duration of asthma, duration of remission, present therapeutic score, past severity, duration of BDP use, initial threshold to methacholine, change in threshold to methacholine, $FEV_{1.0\%}$, blood eosinophil count and serum IgE value.

Asthma exacerbation was defined as the use of a bronchodilator more than three times per day or the use of another anti-asthma drug for 2 consecutive days or rapid deterioration of symptoms. Compliance with anti-asthma drug therapy, asthmatic condition and the subjects' daily asthma diaries were evaluated every 2 weeks. The asthmatic condition was assessed daily and was based on the asthma diary and asthma symptom score as follows: severe attack, 9 points; moderate attack, 6 points; minor attack, 3 points; and occasional wheezing, 1 point. Past asthma severity was derived from clinical charts based on admission history (4 for frequent or severe attacks; 3 for occasional or moderate attacks; 2 for few or mild attacks; 1 for none or mild attack). The present therapeutic score before discontinuing the inhaled corticosteroids was defined as the sum total of all anti-asthma drugs used in a period of 1 month based on the Japanese Society of Pediatric Allergy and Clinical Immunology guidelines (Table 1).[19]

Pulmonary function and inhalation provocation test

Patients were requested to discontinue all anti-asthma drugs for at least 12 h before the test. The $FEV_{1.0\%}$, peak

expiratory flow (PEF) and forced vital capacity (FVC) were measured by using an autospirometer (AS-300; MINATO Ltd, Osaka, Japan). Patients were instructed to measure their PEF twice daily by using peak flowmeters. The PEF variability was calculated as follows:

$$\text{Daily PEF variability}(\%) = ((\text{PEF maximum} - \text{PEF minimum})/\text{mean PEF}) \times 100$$

We evaluated mean PEF variability each month as an indicator of pulmonary function.[20] Bronchial sensitivity was measured using an Astograph (TCK-6100H; Chest Corp., Tokyo, Japan), a direct-writing recorder of the dose–response curve for respiratory resistance (Rrs) during continuous inhalation of methacholine at stepwise incremental concentrations.[21] The test was done in the following manner: Rrs was measured by the forced oscillation method. Two-fold increasing concentrations of methacholine chloride diluted in physiologic saline from 0.049 to 25 mg/dL, were inhaled. The Rrs increased gradually with increasing methacholine concentrations. When the Rrs reached twice the initial value or the patient felt dyspnea, salbutamol was administered. The indicator of bronchial sensitivity was the cumulative dose of methacholine (Dmin) at the inflection point where the Rrs began to increase.

Eosinophil cationic protein

Serum ECP levels were measured with a monoclonal antibody-based fluorometric assay (Pharmacia, Uppsala, Sweden).

Statistical analysis

We used the Mann–Whitney *U*-test to analyze the clinical features of the two groups. Logarithmic transformation was used when analyzing Dmin and IgE values. When the changes in $FEV_{1.0\%}$, log Dmin and attack scores were compared between the three groups (maintenance BDP group, exacerbation (+) subgroup and exacerbation (–) subgroup), we applied the repeated measure of analysis of variance with the Greenhouse–Geisser method. Results were considered significant at a P value < 0.05. Multiple comparisons with the Dann-modulus procedure were used for comparisons of initial and subsequent values between the three groups, as well as data during the observation period. Factors attributed to the exacerbation of asthma were analyzed using two-group discriminant function in the no BDP group. The degree of correlation with asthma exacerbations was evaluated by partial correlation coefficients (PCC).

Results

Characteristics of the subjects

There were no significant differences in baseline characteristics, such as duration of no attack, duration of BDP use and initial threshold of methacholine (shown in Table 2) between the maintenance BDP group, whose parents wished to continue BDP ($n = 11$) and the no BDP group, whose parents wished to discontinue BDP ($n = 25$). Twelve of the 25 subjects (48%) in the no BDP group had an exacerbation of symptoms after cessation (from 5 to 12 weeks: mean 8.1 weeks), while there were no exacerbations in the maintenance BDP group during the observation period ($P < 0.01$).

Changes in laboratory findings

Among the laboratory findings 1 month after cessation of BDP, only deterioration of the threshold to methacholine predicted exacerbation in the no BDP group. There were no significant changes with regard to asthma symptom scores between the three groups (repeated-measure ANOVA, $P < 0.001$). Children in the exacerbation (+) subgroup showed increasing asthma symptom scores 2 months after cessation (multiple comparison with Dann-modulus 5% significance (Fig. 1)). As shown in Fig. 2, there was a significant change in the threshold to methacholine in the three groups (repeated-measure ANOVA, $P < 0.001$). The Dmin in the exacerbation (+) subgroup deteriorated significantly from 2.25 ± 0.89 units to 0.37 ± 0.10 units. Expressed logarithmically, it decreased from -0.13 ± 0.22 to -0.69 ± 0.16 1 month after cessation of BDP (multiple comparison with Dann-modulus, 5% significance). There were no significant changes in the threshold to methacholine in the maintenance BDP group or in the exacerbation (–) subgroup (from 1.71 ± 1.01 units to 2.64 ± 1.18 units and from 2.50 ± 0.73 units to 3.27 ± 1.08 units, respectively; and expressed logarithmically, from -0.233 ± 0.20 to -0.01 ± 0.19 and from 0.11 ± 0.16–0.18 ± 0.17, respectively). When values for the threshold to methacholine were compared between the three groups, there were no significant differences at baseline. However, at 1 month after cessation the threshold to methacholine in the exacerbation (+) subgroup was significantly lower than in the other two groups (multiple comparison with Dann-modulus 5% significance).

Table 2 Characteristics of the 36 subjects

	Maintenance BDP group	No BDP group	*P* value
No. patients	11	25	
Age (years)	12.3 (3.8)	12.6 (4.2)	NS
Gender (Male/Female)	8:3	16:9	NS
Duration of asthma (years)	9.5 (4.1)	9.7 (3.3)	NS
Duration of no attack (months)	8.7 (3.1)	13.3 (10.3)	NS
Past severity of asthma	1.9 (0.7)	2.0 (0.9)	NS
Duration of BDP use (months)	25.7 (15.4)	32.0 (27.0)	NS
Therapeutic score	251.4 (79.6)	261.5 (88.9)	NS
Serum IgE (U/mL)	1234 (208)	1050 (233)	NS
$FEV_{1.0\%}$	82.5 (6.7)	83.6 (5.7)	NS
Initial threshold to methacholine (unit)	1.72 (3.38)	2.38 (2.79)	NS

Baseline characteristics of 36 subjects. Data are the mean (SD). The two groups were compared using the Mann–Whitney *U*-test or Fisher's exact probability test. Results were considered significant at $P < 0.05$. BDP, beclomethasone dipropionate; FEV, forced expiratory volume.

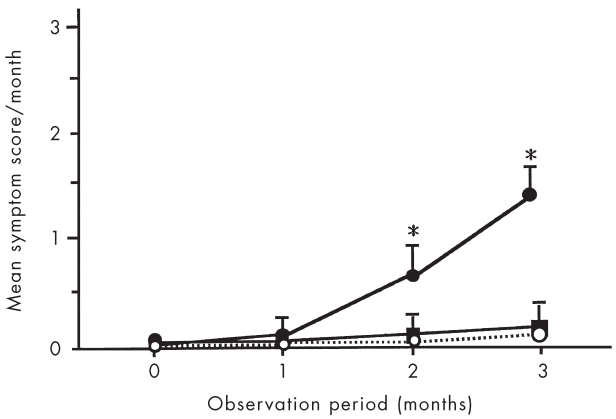

Fig. 1 Asthma symptom scores for the no beclomethasone dipropionate (BDP) groups with (●; $n = 12$) and without (■; $n = 13$) exacerbation and the maintenance BDP group (○; $n = 11$). Data are the mean and SEM of the score points. During the observation period, there was a significant difference in asthma symptom scores between three groups (repeated-measurement ANOVA, $p < 0.001$). After 2 months, asthma attack score from baseline increased significantly among the subjects in the discontinued group with exacerbation (*multiple comparison 5% significance).

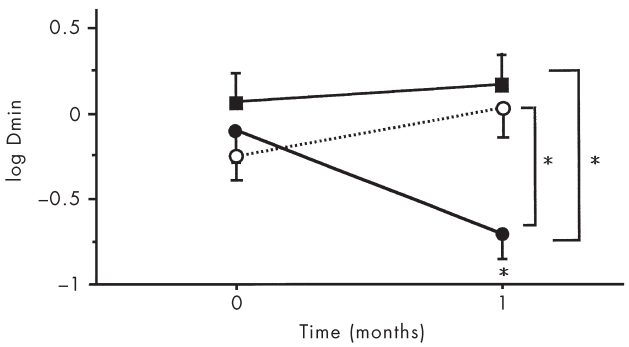

Fig. 2 The minimum dose of methacholine (log Dmin) were evaluated as the indicator of bronchial sensitivity. There was a significant difference in threshold to methacholine among the three groups (repeated-measurement ANOVA, $p < 0.001$). The bronchial sensitivity of the subjects in the discontinued group with exacerbation (●; $n = 12$) decreased significantly from baseline 1 month after cessation of beclomethasone dipropionate (BDP) (*multiple comparison 5% significance), whereas there were no significant changes in the on-maintenance group (○; $n = 11$) and the no exacerbation subgroup (■; $n = 13$). The threshold to methacholine at 1 month was significantly lower in the discontinued group with exacerbation compared with the other two groups (*multiple comparison 5% significance).

There were no significant differences with regard to the $FEV_{1.0\%}$ between the three groups (repeated-measure ANOVA, $P = 0.82$). There were no significant differences in the mean variability of PEF before and at 1 month after cessation of BDP (from 5.09 ± 3.07% to 5.69 ± 4.14%, repeated-measure ANOVA, $P = 0.691$) in the exacerbation (+) subgroup. Eosinophil counts and serum ECP levels did not differ significantly before and at 1 month after cessation of the therapy, even in the exacerbation (+) subgroup ($n = 9$, from 528.5 ± 378.1 /mm^3–585.4 ± 346.8 /mm^3 and from 19.7 ± 7.5 μg/mL to 27.2 ± 15.2 μg/mL, respectively; repeated-measure ANOVA, $P = 0.67$ and $P = 0.24$, respectively).

Factors correlating with exacerbation

Possible predictive factors were then analyzed by using the two-group discriminant function. Variables with high PCC with exacerbations are shown in Table 3: long duration of asthma (PCC = –0.5627), deterioration of threshold to methacholine (PCC = 0.5547), gender

Table 3 Correlation between patient background and asthma exacerbation

Explanatory variables	PCC
Duration of asthma	– 0.5627*
Change in threshold to methacholine	0.5547*
Gender	– 0.5500*
Therapeutic score	– 0.5461*
Eosinophil count	0.4303
Duration of BDP use	– 0.4275
Past asthma severity	0.4258
$FEV_{1.0\%}$	– 0.4235
Initial threshold to methacholine	0.3276
Serum IgE	0.1367
Duration of remission	0.1210
F value	0.0306
Probability of error	0.0622

Two-group discriminant function with regard to the factors implicated in asthma exacerbation.*Results were considered significant at 5% I.P.C.I > 0.5140. PCC, partial correlation coefficient; BDP, beclomethasone dipropionate; FEV, forced expiratory volume.

(female: PCC = –0.5500) and high therapeutic score (PCC = –0.5461). Significance ($P < 0.05$) was defined when the absolute value of PCC was greater than 0.5140 (probability of error, $u = 0.0622$, $F = 0.0306$).

Discussion

Inhaled corticosteroids, such as BDP, are known to reduce bronchial sensitivity and are widely used for treating asthma associated with eosinophilic inflammation of the bronchi.[4–6] Early treatment with inhaled corticosteroids has recently been reported to be effective even in childhood asthma.[7] However, adverse events associated with the long-term use of corticosteroids, such as BDP inhalers, are still controversial.[8–11] Recent treatment guidelines emphasize the importance of regular monitoring to control asthma with minimum of medication.[20] Here, we have tried to determine at what point the clinician can discontinue BDP therapy in asthmatic children who have remained stable for at least 6 months (13.3 ± 10.3 months).

In the no BDP group, 48% of patients developed exacerbations, as opposed to none in the maintenance BDP group ($P < 0.01$). These results indicate that airway hyperresponsiveness did not resolve after 6 months of remission and support the findings of other reports that inhaled corticosteroids suppress the underlying mechanism of asthma, but do not cure the disease.[17] It has been reported that bronchial sensitivity returns to pretreatment levels within 1–2 weeks after a course of 6–8 weeks of 400–800 μg budesonide.[14,15] However, others have reported that the sensitivity remains unchanged for at least 3 months after cessation of a course of 1 year of 400 μg budesonide.[16] An increase in sputum production is one of the first symptoms encountered in asthmatic patients who worsen after discontinuing inhaled corticosteroids, suggesting that inflammation persists even during asymptomatic periods.[16] Therefore, we evaluated the degree of cough, sputum and occasional wheezing or stridor in order to assess mild asthmatic symptoms in children. We found that the threshold to methacholine deteriorated before symptoms developed. We believe that the initial inflammatory changes occur at the mucosal level and include an increase in output from the mucous glands, along with microvascular leakage and edema. This cascade may lead to airway narrowing and changes may increase bronchial sensitivity.[22] Corticosteroids have been reported to reduce epithelial damage, vascular leakage and the recruitment of inflammatory cells such as eosinophils.[23] Serial measurements of serum ECP[24] and PEF variability[25] have been reported to be useful for evaluating asthma. However, in the present study, $FEV_{1.0\%}$, PEF variability, eosinophil counts and serum ECP levels at 4 weeks after the cessation of BDP were not useful; only a change in the threshold to methacholine was found to predict an exacerbation.

We examined the characteristics of patients whose symptoms worsened after discontinuation of BDP and found correlation with the following factors: deterioration of the threshold to methacholine, high therapeutic score, long duration of asthma and female gender. These factors should be considered before inhaled corticosteroid therapy is discontinued.

We conclude the therapeutic effect of inhaled steroids can be maintained for approximately 1 month after they are discontinued. Therefore, cautious reduction is indicated for children in remission. Furthermore, the methacholine inhalation test and patient's profile should be used when clinically stable asthmatic children or their parents wish to discontinue inhaled corticosteroids. Further long-term studies are necessary to evaluate the influence of seasonal and non-seasonal allergen exposure,[26] viral respiratory infections[27] and sinusitis[28] in the management of steroid withdrawal.

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