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The Treatment of Difficult Atopic Dermatitis in Childhood with Oral Beclomethasone Dipropionate

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Beclomethasone dipropionate (BDP) is a synthetic glucocorticoid with great topical potency. It has previously been demonstrated to be an effective treatment for childhood atopic dermatitis (AD) when given orally. We have monitored linear growth and adrenal function in a group of children treated with oral BDP for severe AD. Stable control of disease was achieved in 10/14 patients (mean dose: 1000 μg/day, range 800–1800). At this maintenance dose, there was evidence of deceleration of linear growth in 7/10 patients. There was no significant difference between pre-treatment 8 a.m. plasma cortisol levels and those on the maintenance dose. However, there was a reduction in 24-hour urinary cortisol excretion during maintenance treatment, although this did not reach statistical significance. We regard oral BDP as a useful treatment in widespread childhood atopic AD that has not responded adequately to topical therapy. However, it is mandatory that growth be monitored carefully during its use. ***Key words: Beclomethasone Dipropionate (BDP), Atopic Dermatitis (AD).***

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INTRODUCTION

Beclomethasone 17, 21-dipropionate (BDP) is an extremely potent synthetic glucocorticoid designed for topical use in the lung. Its topical potency on human skin is about 500-fold that of hydrocortisone 21-acetate and about 600-fold that of dexamethasone [1]. BDP was developed as a treatment for asthma and found to achieve good control of symptoms without the unwanted effects associated with the systemic administration of conventional corticosteroids.

Following the observation that AD concurrently improved in a group of asthmatic children treated with inhaled BDP, a clinical trial was undertaken to establish the therapeutic potential of BDP in the treatment of atopic dermatitis [2]. In this study, combined nasal and oral BDP in a total daily dose of 1200 μg was associated with substantial improvement in disease after 4 weeks' therapy.

Since that trial, it has been our practice to consider the use of oral BDP for children with widespread AD which is unresponsive to standard topical treatment. We now prefer an initial dose of 1800 μg/day in three divided doses, and have dispensed with the nasal dose.

MATERIALS AND METHODS

Children with persistent, extensive, non-exudative AD were considered for oral BDP therapy if the following criteria were fulfilled:

(i) their disease had failed to respond to standard topical therapy with emollients and mild topical corticosteroids, undertaken with compliance;
(ii) their age was in the range 2–10 years for girls, 2–11 years for boys;
(iii) their height lay on or above the 10th centile; and
(iv) they had not received oral, inhaled or nasal corticosteroids for a total period greater than 4 weeks during the previous year.

The study group comprised 15 children (7 female, 8 male) with a mean age of 5.7 years (range 1.8–10.9). The median total IgE was 19.954 kU/l (79–68,300).

Before starting treatment, baseline studies were undertaken, comprising a 24-hour plasma cortisol profile and 24-hour urine collection for free urinary cortisol. All patients were then started on oral BDP 1800 μg daily in three divided doses of 600 μg. Each dose was prepared by dispersing the contents of three 200 μg Becotide Rotacaps® in about 20 ml of water. If the therapeutic response was judged to be clinically useful after 4 weeks, the dose of BDP was then gradually reduced over a 6 week period, with the aim of reaching a maintenance dose for each child. Parents were asked to seek a dose which permitted acceptable social and educational function and and relatively undisturbed sleep.

After a 6 month period on this maintenance dose, the cortisol studies were repeated. The patients were assessed throughout the study using standard score charts for AD [3], and their weight and height were recorded by the same observer. Each child's height after 6 months of maintenance treatment was compared with height prior to treatment by calculating the Standard Deviation (SD) score on each occasion. Normal values for height SD scores have been published previously by Tanner et al. for children over the age of 2 years [4, 5].

RESULTS

Fourteen of the 15 children demonstrated substantial benefit after 4 weeks' treatment at the initial starting dose of BDP. 10 of the 14 were able to reduce the dose to a maintenance level at which acceptable control of disease was retained. The mean maintenance dose was 1000 μg (range: 800–1800), after a mean duration of treatment of 14.5 months (range: 8–21 months). Four children failed to maintain their initial treatment response and oral BDP was therefore withdrawn. Most parents reported improvement in itching and sleeping within 2 weeks of starting treatment.

In the group of 10 children who reached a satisfactory maintenance dose, 3 continued to grow normally along their centile for height after 6 months at this dose level, according to their growth charts. The remaining 7 children all showed some evidence of growth impairment. As one child was less than 2 years of age at the start of treatment, SD scores could not be calculated, and are therefore available for only 9 of the 10 children. These scores are shown in Fig. 1. For the group, the pre-treatment median height SD score was +0.285 (95% confidence intervals −0.295 to +1.055) and the post-treatment median score was −0.390 (95% confidence intervals: −0.94 to

+0.465). The reduction is statistically significant (95% confidence intervals for the difference in medians: 0.3 to 1.03, Wilcoxon Signed Rank Test).

There was a slight reduction in the 8 a.m. plasma cortisol values after 6 months on the maintenance dose, compared with pre-treatment levels, which did not achieve statistical significance: pre-treatment median value 400 mmol/l (95% confidence intervals: 319–538) and median value on maintenance treatment 372 mmol/l (95% confidence intervals: 269–467), (95% confidence intervals for the difference in medians: −70 to 172.5, Wilcoxon Signed Rank Test).

The lowest level of sensitivity for the measurement of 24-hour free urinary cortisol excretion in our laboratory is 25 nmol/24 h. Therefore values expressed as < 25 nmol/24 h have arbitrarily been given the value 25 nmol/24 h for the purposes of statistical analysis. By this analysis, the median 24-hour urinary free cortisol was reduced from 32.5 (95% confidence intervals: 26.5–40.0) to 25.0 nmol/24 h (95% confidence intervals:. 25.0–31.5) after 6 months of maintenance treatment (95% confidence intervals for the difference: −3.75 to 15.0, Wilcoxon Signed Rank Test).

DISCUSSION

The lack of adverse systemic effects of corticosteroid type in children inhaling BDP for asthma is probably related to its rapid metabolic inactivation. When given orally, BDP is rapidly broken down to inactive metabolites by the liver and excreted in the faeces via the bile. Of the metabolites formed, beclomethasone 17-monopropionate has some glucocorticoid activity, but the major final metabolite, beclomethasone, is virtually inactive [6].

Studies in adults show that up to 90% of an inhaled dose is swallowed, of which some 70% is absorbed via the gastrointestinal tract [6].

A study of adrenal function in asthmatic children treated with inhaled BDP has shown a dose-related effect of BDP on cortisol excretion as the dose increases from 200–800 μg/day [7]. In our patients, we observed a small reduction in 8 a.m. plasma cortisol values, though all values fell within our normal range. We also observed a small reduction in 24-hour urinary cortisol excretion. These reductions failed to reach statistical significance, but the numbers of patients studied was small. In the case of the 24-hour urinary cortisol measurements, all initial values were less than the lower limit for normal values (50–200 nmol/24 h). This suggests that our patients were already subjected to a degree of adrenal suppression, possibly reflecting percutaneous absorption of topically applied corticosteroids. The normal pre-treatment 8 a.m. plasma cortisol results imply that this test is less sensitive to such subtle degrees of adrenal suppression. Our findings suggest that treatment with oral BDP in this dose range is likely to be associated with a degree of adrenal suppression. However, it is difficult to isolate the possible contribution made by topical treatment, though our patients were generally using less when on maintenance treatment with BDP than they had previously. The clinical relevance of the changes we observed is not known.

When used as a treatment for asthma in children, linear growth has been reported to progress at a normal rate at daily doses of 600 μg BDP before puberty, and 400 μg BDP during puberty [8]. When used as a treatment for AD, we find that the dose required for effective maintenance therapy is usually at least 800 μg per day, and the finding of a significant reduction in height SD scores in our patients suggests that larger doses may have a greater effect on linear growth. It should be stressed that we observed none of the other well known adverse effects associated with oral glucocorticoids, such as increased appetite, weight gain or hypertension.

We regard oral BDP as an effective therapy for difficult atopic AD in childhood, but anyone contemplating this treatment approach should be aware that it may be associated with decreased linear growth, particularly at doses in excess of 800 μg/day. Any child treated with oral BDP should in our view:

(i) have a pre-treatment height above the 10th centile,
(ii) be at least 2 years old and pre-pubertal (i.e. less than 11 years old in the case of females, and less than 12 years old in the case of males),
(iii) have regular monitoring of growth during therapy,
(iv) be discontinued at the age at which the onset of puberty is expected, to allow both catch-up growth and the normal pubertal accleration in growth.

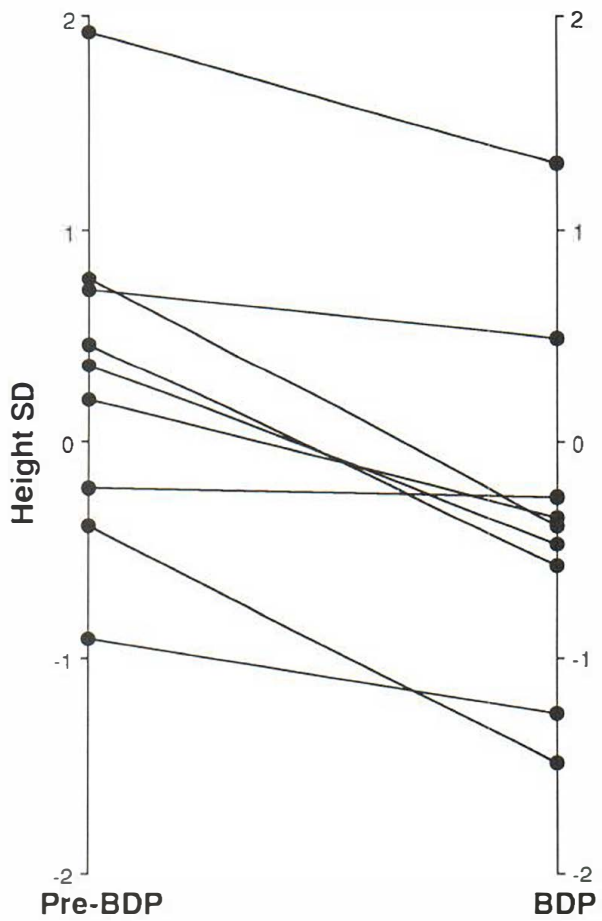

Fig. 1. Height standard deviation (Height SD) scores before treatment with BDP and after 6 months on a maintenance dose.

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