Overnight urine growth hormone, cortisol and adenosine 3' 5' cyclic monophosphate excretion in children with chronic asthma treated with inhaled beclomethasone dipropionate

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Overnight urine samples were obtained from 34 asthmatic children, 24 of whom were receiving inhaled beclomethasone dipropionate (BDP), and 30 controls. The urine volume of the children receiving inhaled steroids was significantly greater than that of the other asthmatic children and of the controls (P<0.05). Urine growth hormone was within the normal range for all of the subjects and there was no demonstrable relationship between urine growth hormone and height or height standard deviation score. Urine steroid output was significantly reduced in the BDP receiving group when the results were expressed in U l⁻¹ but there was no difference between the groups when the results were expressed per specimen. Urine adenosine 3' 5' cyclic monophosphate (cAMP) results were similar for all groups. We conclude that use of BDP increases overnight urine volume but, in our study, does not appear to influence the output of urine cortisol. Urine free cortisol measurements may not be a very sensitive tool for the detection of small changes in endogenous steroid production. The use of BDP does not adversely affect the output of urine growth hormone.

Introduction

Inhaled glucocorticosteroids are one of the most useful and controversial medications used in the management of childhood asthma. The extent to which topical steroids are systemically absorbed is of primary concern.

Systemic adsorption may result in hypothalamic-pituitary-adrenal suppression thereby causing reduction or alteration in endogenous steroid production or by adversely affecting growth (1), by some alternative mechanism.

Much conflicting information has been published about the relative safety of inhaled steroids. This reflects the diverse populations selected and the methods used to assess them.

Children who suffer from chronic asthma may be shorter than normal. Causes of poor height growth other than glucocorticosteroids may include stress caused by hypoxaemia, especially during sleep, and abnormal production or sensitivity to endogenously produced growth hormone (2). Reduced energy intake and increased energy expenditure associated with the increased work of breathing during episodes of acute respiratory distress may also influence growth.

The aim of this study was to define a group of children with comparable severity of asthma and to look at the relationships between height growth, inhaled steroid usage and endogenous steroid production. We also studied their overnight growth hormone production and output of adenosine 3' 5' cyclic monophosphate (cAMP), an index of short term stress.

Methods

Thirty-four children (nine girls and 25 boys) suffering from chronic perennial asthma participated in the study. Twenty-four of the children were taking regular inhaled steroid therapy. Thirty healthy school children (17 girls and 13 boys) were recruited as controls. Local ethical committee approval was obtained for the study and informed consent was given by the participants’ parents.

The asthmatic children were recruited from paediatric outpatient clinics at Southampton General Hospital.

Each asthmatic child kept a standard asthma diary for 28 days. They recorded the best of three attempts at
peak expiratory flow rate (PEFR) on rising in the morning before using any medication and again at night before going to bed. The Wright's mini-flow meter was used to record all readings. All medication taken was recorded. Twenty-four of the children were receiving regular inhaled glucocorticosteroid therapy. All of these patients had been treated with beclomethasone dipropionate for a minimum of 3 months. By means of the diaries the number of days on which the PEFR was less than 75% of the predicted value and the number of days when the diurnal variation was greater than 25% of the predicted value was calculated. All of the asthmatic children took inhaled bronchodilators. None of them took oral theophylline.

The children were weighed, and measured using a stadiometer. Their height standard deviation score and their surface areas were calculated (10).

The children were all continent of urine at night. When they had completed the asthma diaries they were asked to collect a timed overnight urine specimen. The urinary creatinine concentration of each specimen was determined using the Jaffe alkaline pyruvate technique. Urinary free cortisol was measured by specific radioimmunoassay (11) with a detection limit of 8 nmol l⁻¹ and a between batch precision ranging from 12-6 to 15-2% for the low, median and high controls. cAMP was analysed with the bovine adrenal protein kinase competitive binding method (12); between batch precision was 13-2 and 13-9% for low, median and high controls. The overnight output of urinary human growth hormone was measured using an assay described by Evans et al. (13). The method will detect 0-5 µU l⁻¹ urine with between batch precision of 5-5-16-9% for low, median and high controls.

Results

The children suffering from asthma had a mean age of 8-55 years (6-69-10-76). The mean age of the control children was 9-00 (7-52-10-88) years. All of the children had a puberty rating of 1 on a physical examination (14).

The mean dose of beclomethasone dipropionate was 341 µg d⁻¹ (range = 200-1200 µg).

The number of days on which the PEF was less than 75% of the predicted peak flow was not significantly different for the children receiving steroids compared with the asthmatic children not taking steroids. Similarly no significant difference was found between the groups for the number of days when the diurnal variation was more than 25% of the predicted peak flow. This suggests that the severity of disease was comparable for the two groups of asthmatic children during the study period. The records of inhaled β-agonist usage were not accurate, additional doses taken during the day were infrequently recorded. The results were not analysed.

Urine volume was measured for each patient. The mean volume for the control children was 220 ± 106 ml (mean ± SD) per overnight collection. The volume for the asthmatic children who were receiving BDP was 300 ± 120 ml and for those children with asthma but not on BDP the volume was 180 ± 56 ml. Non-parametric analysis using the Mann–Whitney U-test revealed a significant difference between those receiving BDP and the controls (P < 0.05) and asthmatics not on BDP (P < 0.05). This result has an important influence on the interpretation of the subsequent data.

When urine creatinine expressed as mmol l⁻¹ was compared there was a highly significant difference between those asthmatics on BDP and those who were not (P < 0.01). There was no significant difference between the lean body mass of these two groups. However, when the difference in urine volume was taken into account and the results were expressed as an amount per specimen there was no difference between the groups.

The urinary cortisol concentration was also expressed both as an amount per litre and per specimen. Urine cortisol expressed as an amount per litre showed a significant difference between those asthmatic subjects receiving BDP and those who were not (P < 0.01). When the values for children receiving BDP were compared with the controls again the difference was marked (P < 0.01). However when the amounts of urinary cortisol per overnight specimen were compared it was not possible to show any difference between the groups.

We went on to explore the relationship between the concentration of urinary free cortisol both per specimen, and per litre, with the dose of BDP taken in 24 h. We were unable to show any significant correlation between the dose of BDP administered either in absolute terms or as an amount per square metre of surface area, or per kilogram of lean body mass, or per kilogram of body weight.

Urinary cAMP was measured in the urine samples. No significant difference was noted when the samples from asthmatic children were compared with those from the controls if the results were expressed as a concentration per litre. There was a significant difference when the results from asthmatics taking BDP was compared with those who were not (P < 0.5) but this disappeared when the amount of cAMP per specimen was compared.
Analysis of urinary growth hormone concentration per specimen showed no difference between the two groups of asthmatic children. All of the results fell within the normal range established for prepubertal children for this laboratory (15). There was no correlation between height standard deviation scores and the overnight urine HGH concentration.

Discussion

Inhaled steroids have proved to be a useful adjunct in the management of childhood asthma. Whilst their therapeutic value is proven significant doubts still exist about the extent to which they are systemically absorbed.

It has been shown that inhaled beclomethasone dipropionate is to some extent absorbed. Serial serum sampling has been used to demonstrate that the overall production of endogenous steroid is diminished (16). The clinical significance of these observations is less certain.

Asthma is associated with an altered pattern of linear growth. Recently a distinctive pattern has been described. Children appear to gradually fall away from their predicted height centile as they approach puberty. The onset of sexual maturation is delayed hence the duration of growth is prolonged and for the most part they ultimately attain their predicted adult height. The cause of this pattern of growth has been the subject of much speculation (17,18).

The children that we studied were felt to be suffering from similar severity of asthma symptoms at the time of their entry into the trial. The use of anti-asthma medications, in particular anti-inflammatory drugs will inevitably influence the course of the underlying disease so that whilst symptoms appeared to be of comparable severity at the time of the study it would be highly speculative to comment upon the inherent severity of the disease itself. This fact may contribute to the discrepancy in the height of the two groups of asthmatics. Since there are no reliable clinical indices of the inherent severity of asthma, cross sectional studies of growth are never easy to interpret.

Abnormal production of human growth hormone has been postulated as the cause of growth delay in asthma. Growth hormone stimulation tests have failed to yield abnormal results (6). In this study we chose to measure unstimulated growth hormone production. We showed no demonstrable relationship between the output of hormone and linear growth or the use of inhaled steroids. Reduced sensitivity to or production of growth cofactors still remain to be investigated.

Poorly controlled asthma is associated with an increase in nocturnal symptoms. Episodic drops in oxygen saturation as well as frequent disturbance of sleep may give rise to short term stress (5). Cyclic AMP has been used as an index of stress in patients who have suffered thermal burns (19). It may be measured in urine specimens. The output of cAMP is unaffected by diet or by the use of theophyllines but can be increased by β-agonists (20,21). However, when β-agonists are used regularly the rise in output of cAMP is considerably less marked (22). We were unable to show any difference in the production of cAMP between the asthmatic and control subjects. This suggests that our asthmatic children were, as their diaries suggested, reasonably well controlled for the duration of the study.

Finally, we attempted to re-explore the relationship between the use of inhaled steroids, suppression of the hypophyseal-pituitary-adrenal axis, and growth retardation. This subject has been investigated by many groups in the last 20 yr with results often at variance from one another. Previous studies can be roughly divided into those which use early morning plasma cortisol level with or without short term tetracosactrin tests, and those that use the output of urine steroids.

Interpretation of these studies is complicated by variations in the inhaled steroid used and whether or not the subjects were receiving the medication for the first time and the use of oral steroids. Studies using the output of urinary steroids more consistently appear to show suppression by inhaled steroids (3,24,25).

In this study we chose to use an overnight urine collection. The indefinite period of this collection is a disadvantage but since the duration of sleep, and hence circadian rhythm is subject to individual variation it was felt that this period of time reflects the output of hormones that are influenced by diurnal variations.

We showed that the children taking inhaled BDP had significantly greater overnight urine volumes than either the control children or those asthmatics not taking steroids.

We failed to demonstrate any difference in the production of urinary cortisol between asthmatic subjects receiving BDP and either those children taking only inhaled salbutamol or the healthy controls. If the results are expressed as cortisol: creatinine ratios or as concentrations of cortisols per litre then it is possible to show differences. However, it should be borne in mind when interpreting these results an optimal sample size of more than 200 subjects would ideally be required to demonstrate differences in the cortisol:creatinine ratio. Few existing studies have been performed on this scale.

As with all glucocorticosteroids BDP has a potential mineralocorticoid effect. Since there was no evidence that there was a significant difference in the severity of
symptoms between the two groups it is likely that changes in the urine output of those children taking BDP were a consequence of the systemic effects of inhaled steroids.

Urinary free cortisol measurement may not be a sufficiently sensitive test to reveal small differences in net cortisol production. Indeed it was designed as a test of states of excess rather than deficiency (23). Glucocorticosteroids also have a permissive action directly on the kidneys affecting the control of diuresis and concentration.

There is no doubt that some children who suffer from asthma fail to grow at the anticipated rate during childhood. The causes of this observation remain obscure and it seems likely that no one single factor can be incriminated.

References