

## Adrenal function in asthma

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### Abstract

A dose dependent suppression of daily cortisol excretion was shown in 25 children with asthma being treated with beclomethasone dipropionate. Cortisol metabolites tended to occur below the normal range when doses of beclomethasone of more than 400  $\mu\text{g}/\text{m}^2/\text{day}$  were given. Androgen excretion below the normal range was apparent in asthmatic children aged 8-13 years regardless of whether they were receiving inhaled steroids. This may be the reason for growth delay often seen in asthmatic children. These side effects of beclomethasone are not enough reason to discourage its prescription for the treatment of asthma, but endocrine assessment is desirable when the dose exceeds 400  $\mu\text{g}/\text{m}^2/\text{day}$ .

Because inhaled steroids are used for the treatment of childhood asthma, there have been many studies of their systemic side effects.<sup>1</sup> Several of these have shown that hypothalamic-pituitary-adrenal function remains normal when low doses of inhaled steroids are used ( $<400 \mu\text{g}/\text{day}$ ),<sup>2-4</sup> but there is evidence that suppression occurs if the doses are increased ( $>400 \mu\text{g}/\text{day}$ ).<sup>5-8</sup> Most of these studies, however, have used pharmacological stress tests, rather than measuring basal adrenal state or the response to natural stresses.<sup>2-4, 7, 8</sup> Single or intermittent measurements of plasma cortisol concentration have been reported, but they are difficult to interpret because of normal daily fluctuations and the wide normal range. The 24 hour urinary free cortisol output has also been used but is unreliable for the diagnosis of adrenal insufficiency.<sup>9</sup> Measurement of total cortisol metabolite excretion during a 24 hour period, especially after the correction for body size, has been recommended as an alternative, non-invasive, and easily repeatable indicator of basal adrenocortical activity.<sup>9</sup>

Concerns have been expressed that any adverse effect on growth could be the result either of the use of inhaled steroids or of the asthma itself,<sup>10-15</sup> and the relative contributions of these two factors to growth delay are not fully understood.<sup>11, 12</sup> As androgens also have a role in growth, reduced adrenal androgen production could also contribute to the pathogenesis of growth delay among asthmatic children.<sup>16, 17</sup>

The aim of this study, therefore, was to investigate adrenal function in asthmatics, half of whom were receiving inhaled steroids, by measuring 24 hour urine total cortisol metabolite excretion. In addition, the excreted androgen metabolites were measured to see whether androgen production correlated with growth and growth velocity.

### Patients and methods

Forty eight children (18 girls and 30 boys) with chronic asthma took part in the study. Forty one of

them attended our outpatient clinic for asthmatic children, the remainder were recruited from a local health centre. The subjects in group 1 (nine girls and 14 boys, aged from 5.2 to 14.5 years, median 8.7) had never received inhaled steroids, but 13 of them were taking inhaled sodium cromoglycate regularly. The subjects in group 2 (nine girls and 16 boys, aged from 4.8 to 14.5 years, median 9.9), were receiving inhaled beclomethasone dipropionate 200-900  $\mu\text{g}$  daily (median 400  $\mu\text{g}$ ), or 140-930  $\mu\text{g}/\text{m}^2$  body surface area (median 420  $\mu\text{g}/\text{m}^2$ ). They had inhaled beclomethasone through conventional inhalation devices for one to eight years (median three). None of them had been treated with systemic steroids for more than 10 days continuously during the previous two years, none had received any during the previous three months, and none was using topical steroids. They were all continent of urine day and night. Each child was followed up for 30 days using a standard diary card to record any symptoms and the drugs used during this period. Peak expiratory flow rates were recorded each morning and evening to make sure that the subjects' asthma was well controlled. At the end of the 30 day period a 24 hour urine sample was collected. The samples were analysed for total cortisol androgen metabolites by gas chromatography.<sup>17</sup> The following principal metabolites of cortisol and cortisone were determined: tetrahydrocortisone, tetrahydrocortisol, allotetrahydrocortisol,  $\alpha$  cortolone,  $\beta$  cortol and  $\beta$  cortolone, and  $\alpha$  cortol, and the individual results summed to give a total cortisol metabolite excretion rate. The sum of tetrahydrocortisol and allotetrahydrocortisol excretion rates give a figure for cortisol metabolite excretion. The androgen metabolites that were measured were androsterone and aetiocholanolone. Urinary creatinine was also measured, but the results were only included if the creatinine content was in agreement with that which would be expected from the child's body surface area.

Height was measured with the Harpenden stadiometer and the previous year's height was obtained from the medical records. These measurements were made with the same stadiometer as on previous attendances at the outpatient clinic. The height standard deviation (SD) score was used to compare children's height independently of their age and sex.<sup>18, 19</sup> Data about puberty were not available.

The correlation between dosage and excretion rates of cortisol metabolites was evaluated by the Spearman rank correlation test. Multiple regression analysis was carried out to assess the correlation between dosage, duration of treatment, and cortisol metabolites excretion rates. The unpaired *t* test was used to compare the significance of differences among the height SD scores.

### Results

All the children in group 1 had a 24 hour cortisol

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metabolite value for body size within the normal range (unpublished observations) whereas eight of the children in group 2 showed low values (fig 1). There was a significant negative correlation between the cortisol metabolite excretion and the dose of inhaled beclomethasone/body surface area ( $r_s = -0.4828$ ,  $p = 0.014$ ) (fig 2). Cortisol excretion was clearly suppressed in eight of the children who were treated with beclomethasone in doses of  $>400 \mu\text{g}/\text{m}^2/\text{day}$  (fig 2). There was also a highly

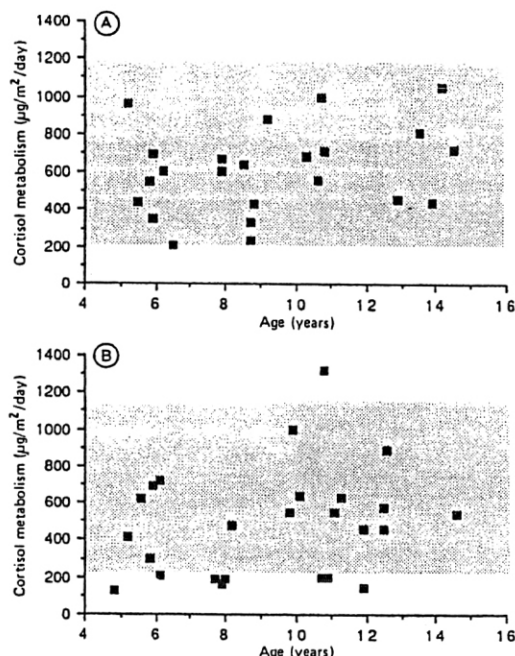


Figure 1 Twenty four hour values for cortisol metabolite, body size, and age, in group 1 (A) and group 2 (B). The shaded areas represent the normal range.

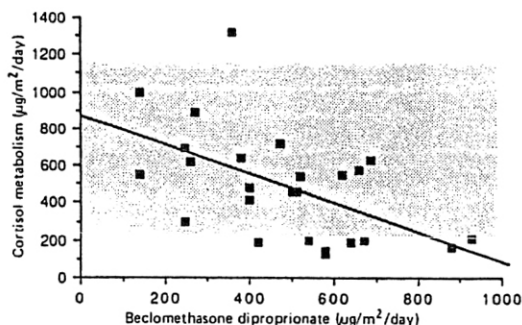


Figure 2 Twenty four hour values for cortisol metabolite and dose of beclomethasone dipropionate for body size. The correlation is significant. The shaded area represents the normal range.

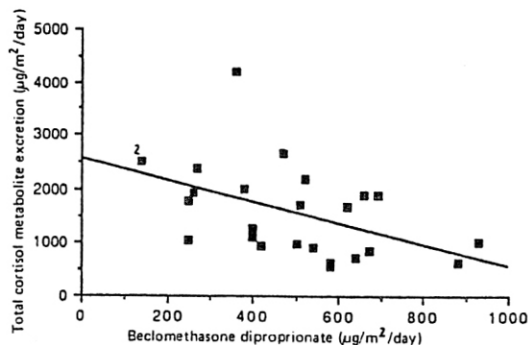


Figure 3 Twenty four hour values for urinary excretion of total cortisol metabolites and dose of beclomethasone dipropionate for body size. There is a highly significant negative correlation.

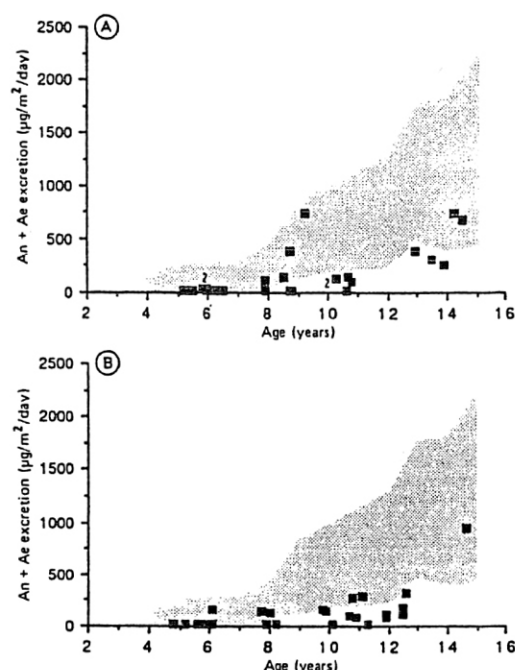


Figure 4 Twenty four hour values for androsterone (An) and aetiocholanolone (Ae) excretion for body size, and age, in group 1 (A) and group 2 (B). The shaded area represents the normal range.

significant negative correlation between the total cortisol metabolite excretion and the dose of inhaled beclomethasone (fig 3). The significance was increased when the beclomethasone was assessed according to dose/body surface area ( $r_s = -0.605$ ,  $p = 0.001$ ) than if it was assessed according to the absolute dose ( $r_s = -0.412$ ,  $p = 0.041$ ). There was no significant correlation between the duration of treatment and total cortisol metabolite excretion, but there was between the dose of beclomethasone and total cortisol metabolite excretion ( $p = 0.014$ ).

Both groups had low values of 24 hour urinary androgen metabolites compared with a normal population (fig 4), but these were not related to the dose of beclomethasone.

The height SD scores for group 1 ranged from  $-1.69$  to  $1.35$  (mean (SD)  $-0.002$  (0.824)) and for group 2 from  $-1.51$  to  $1.22$  (mean (SD)  $-0.012$  (0.668)). there were no significant differences in the height SD scores of the two groups compared with each other or when each was compared with the general population. Previous annual height measurements were only available for 11 of the children in group 1, and only limited reliance can be placed on these, as the initial measurements were made in a health clinic that was not using a stadiometer. Of these, four had height velocities below the 25th centile. In group 2, 11 of 25 children had height velocities below this centile.

## Discussion

These data show that cortisol production is reduced in some but not all asthmatic children after prolonged use of inhaled beclomethasone dipropionate in doses over  $400 \mu\text{g}/\text{m}^2/\text{day}$ . No reduction was apparent in the asthmatic children who were not taking inhaled steroids. There was a significant negative correlation between both the cortisol metabolite and the total cortisol metabolite excretion and the dose of beclomethasone.

The dose dependent effect of inhaled beclomethasone on basal adrenal function has already been shown.<sup>5 6 8 21-23</sup> Two of these studies

showed that this effect was dose dependent in children by measuring the integrated cortisol concentration during a number of hours rather than at a single time point.<sup>5 6 8</sup> In the studies by Law *et al.*,<sup>5 6</sup> this was shown after measurement of nocturnal serum cortisol every 20 minutes from midnight to 0600, although it was not continued during the day to give a more complete picture. Bisgaard *et al.* showed that there was a correlation between the dose and the adrenal cortisol production by measuring the 24 hour free cortisol and cortisol metabolite excretion.<sup>8</sup> They failed to find any effect of inhaled steroids on the response of serum cortisol to a stimulation test with adrenocorticotrophic hormone. Neither of the studies assessed this dose dependent effect according to body surface area, but used absolute dose. In our data the significance was much weaker when the assessment was made according to absolute dose.

Seven asthmatic children out of 13 who were on high doses of inhaled steroids ( $>460 \mu\text{g}/\text{m}^2/\text{day}$  or  $>800 \mu\text{g}/1.73 \text{ m}^2/\text{day}$ ) had low cortisol metabolite excretion rates. In the study by Prah *et al.* a low response to adrenocorticotrophic hormone stimulation was seen only when doses of beclomethasone were  $>2000 \mu\text{g}/1.73 \text{ m}^2/\text{day}$ , and the 24 hour urinary free cortisol excretion was depressed only in three children who were taking 3300, 2800, and  $2450 \mu\text{g}/1.73 \text{ m}^2/\text{day}$ , respectively.<sup>7</sup> According to our method of assessment, however, it seems that basal adrenal function is impaired by smaller amounts of inhaled steroids. It is noteworthy that although only one child from group 2 was taking  $>800 \mu\text{g}/\text{day}$  of inhaled beclomethasone, there were 13 children taking  $>800 \mu\text{g}/1.73 \text{ m}^2/\text{day}$  ( $>460 \mu\text{g}/\text{m}^2/\text{day}$ ), which is considered the upper limit of the conventional adult dose.

We did not find any correlation between the cortisol metabolite or total cortisol metabolite excretion and the length of time that they had been taking beclomethasone. It seems that a short period of use is enough to suppress the adrenal cortex.<sup>21 24 25</sup>

The approach we have used to measure the 24 hour urinary cortisol metabolite excretion has also been used in two other studies. Springer *et al.* analysed the 24 hour tetrahydrocortisone and tetrahydrocortisol excretion by radioimmunoassay.<sup>4</sup> Bisgaard *et al.* measured most of the cortisol metabolites using gas chromatography in a number of cases as we did.<sup>8</sup> Neither study assessed the 24 hour urinary cortisol metabolite excretion with reference to body surface area.

We found low androgen metabolite excretion in both groups of asthmatic children. As it is known that androgens have a role in growth,<sup>16 17</sup> this might be a reason for the growth delay often seen in asthmatic children.<sup>11 13</sup> We did not find any significance between the height SD scores in the two groups. There was also no difference between the height SD scores of the two groups and those of normal children. This means that the asthmatic children we studied were not as a group significantly shorter than normal children. Adrenal androgens would have their maximum impact in growth just before the onset of puberty. Although unfortunately we did not record pubertal staging, we would expect that only half the children that we studied would be in the phase of growth that is regulated by adrenal androgens.

In conclusion, our findings indicate that suppression of basal adrenal function occurs when the dose of inhaled steroids exceeds  $400 \mu\text{g}/\text{m}^2/\text{day}$ .

This side effect is not severe enough to discourage prescription of this treatment for asthma, but assessment of endocrine function is desirable when the dose of beclomethasone exceeds that limit. The cause of delayed growth and puberty often seen in asthmatic children may be attributed to low production of adrenal androgens. It would be of considerable interest to collect further data on asthmatic children with severe growth retardation and relate this to pubertal grading and androgen production.

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