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Urine cortisol excretion in children treated with high doses of inhaled corticosteroids: a comparison of budesonide and beclomethasone

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Urine cortisol excretion in children treated with high doses of inhaled corticosteroids: a comparison of budesonide and beclomethasone. S. Pedersen, G. Fuglsang.

ABSTRACT: Thirty one children with asthma were treated with inhaled beclomethasone and budesonide in a randomized cross-over study of 2 × 6 weeks' duration. The excretion of free cortisol in two 24 hour urine samples, collected at the end of each treatment period, was significantly higher (mean = 76.3 nmol per day) during budesonide treatment than during beclomethasone treatment (mean = 53.7 nmol per day) ($p < 0.01$). The difference between the two drugs was more pronounced in the eight children who received 1000 and 1200 µg per day than in the 22 children who received 800 µg per day. Four children had cortisol excretion below the normal range when treated with beclomethasone. This was seen in one child during budesonide treatment. The age of the child did not influence the result. The long term clinical significance of these findings has yet to be elucidated.

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The introduction of inhaled topically active glucocorticosteroids (GCS), beclomethasone dipropionate (BDP) and budesonide (BUD), has improved the life of many children with severe asthma. Because of the effectiveness of these drugs their use has become more common during recent years and there is an increasing number of milder cases of asthma in children being treated with GCS. Recently, however, BDP was found to have significant, dose dependent adrenal supressive effects in children, when used in doses of 200–800 µg per day [1, 2]. Furthermore, the findings of one of these studies [1] indicated that there might be differences in adrenal suppressive effects between BDP and BUD; BDP being more suppressive than BUD.

The present study was performed to determine whether there are any differences in adverse systemic effects between BDP and BUD in children receiving high dose inhaled therapy with these drugs.

Patients and methods

Fifteen boys and sixteen girls receiving high dose inhaled treatment with either BDP or BUD were studied. Their mean age was 10.2 yrs (range 5–15 yrs). Apart from asthma, all were in good health. None had received oral or intravenous GCS treatment within the previous six months.

The design was an open cross-over study, where the children during two six week periods were treated with inhaled BDP and BUD in randomized sequence. The dose of GCS varied from 800–1200 µg per day (mean = 900 µg per day). It was the same in both periods and was equal to the dose normally used by the child. Inhaled beta$_2$-agonists, slow release theophylline and oral beta$_2$-agonists were kept constant throughout the trial. No other medications were allowed.

The inhaled GCS was given twice daily, in the morning at breakfast and in the evening at dinner. The same delivery system was used in both periods *i.e.* either a metered dose inhaler alone (n = 17) or in combination with a large volume spacer (Volumatic or Nebuhaler; n = 14).

BDP aerosols, 50, 100 and 250 µg per actuation, and BUD aerosols, 50 and 200 µg per actuation, were used. To obtain the same dose in both periods, combinations of aerosols had to be used in some cases (1000 µg per day = two puffs of BDP 250 µg per puff twice daily during one period and two puffs of BUD 200 µg per puff plus two puffs of BUD 50 µg per puff twice daily during the other period).

Forced expiratory volume in one second (FEV_1) was measured at hospital on a Vitalograph® at the end of each treatment period.

Adrenal function was evaluated by the excretion of free cortisol in two 24 hour urine samples collected during the last week-end of each period. Cortisol concentrations were measured by a specific radioimmunoassay. In addition, the excretion of creatinine in the urine was determined in order to evaluate the accuracy of urine collection. The laboratory was blind to the experimental dose regimen.

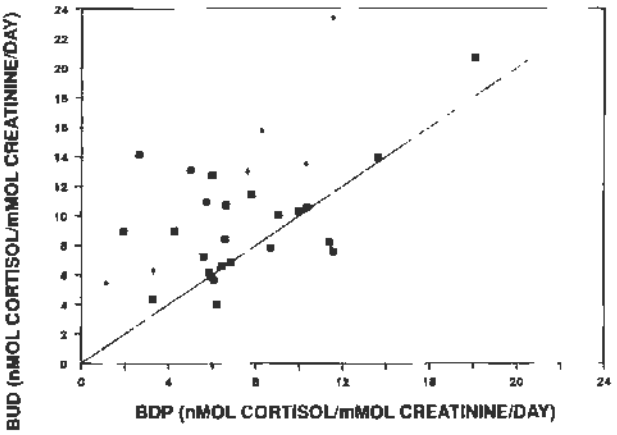

Fig. 1. Urine cortisol excretion standardized for creatinine excretion in thirty children treated with beclomethasone (BDP) and budesonide (BUD) in a randomized cross-over study. Each value represents the mean of two 24-hour urine samples. ■, +, ● = children receiving 800, 1000 and 1200 μg per day, respectively.

Statistics

Wilcoxon's rank sum test was used to compare data from the two periods and $p < 0.05$ was considered statistically significant. Values are given in the text as mean and range.

Results

Thirty children completed the study. One girl was withdrawn because of acute exacerbation of her asthma during the BUD period.

Fourteen children were treated with BDP and sixteen with BUD during the first period. Neither period or carry-over effects were found. The individual daily excretion of free cortisol in the urine during the two periods is shown in figure 1. The excretion of cortisol was significantly higher (76.3 (25–215) nmol per day) during BUD treatment than during BDP treatment (53.7 (6–118) nmol per day) ($p < 0.01$). This was also the case for cortisol excretion standardized for creatinine excretion (10.2 and 7.6 nmol cortisol per mmol creatinine per day respectively; $p < 0.01$). For both parameters the difference was more pronounced in children treated with 1000 and 1200 μg GCS per day than in children treated with 800 μg per day.

The difference in cortisol excretion between the two drugs was not significantly influenced by the age of the child in the 22 children who received 800 μg GCS per day.

FEV_1 measured at the end of each period was 2.35 (0.9–3.8) *l* (BDP) and 2.26 (0.8–3.9) *l* (BUD) (NS).

There was no difference in cortisol excretion between the patients using a large volume spacer (62.7 (6–204) nmol per day) and the patients using a metered dose inhaler alone (66.7 (13–215) nmol per day).

In four children cortisol excretion measured in nmol per day was below the normal range in the BDP period. This was seen in one child during the BUD period. In the remaining cases cortisol excretion was within the normal range.

No side effects were reported.

Discussion

Comparison of clinical effects of BDP and BUD was not the main purpose of our study. Other investigations have found that there are no clinically important differences in anti-asthmatic potency between equivalent doses of the two drugs [3–7]. We concentrated upon evaluating possible differences in systemic side effects between the two drugs. To the best of our knowledge this has only been done in one earlier study in children [1]. The findings of that study indicated a difference in systemic side effects between the two drugs in favour of BUD. However, the difference failed to reach statistical significance, perhaps because only a limited number of patients was receiving BUD ($n = 10$). In the present study a large number of children received both BDP and BUD and under those conditions BDP had a significantly higher adrenal suppressive effect than BUD. Since the cortisol excretion of most BDP children was within the normal range the clinical importance, if any, of this has yet to be elucidated in prospective long-term clinical trials, also evaluating other parameters such as growth, bone mineralization and calcium excretion in the urine. So far no studies have indicated any clinical systemic effect of high dose inhaled GCS, just as patients on such treatment often show steroid withdrawal symptoms and marked improvement in adrenal function when they are weaned off oral steroids [8–10].

Measurement of baseline cortisol excretion from a period without inhaled GCS was not possible in the patients studied and therefore the magnitude of systemic activity of BUD could not be evaluated. However, a pharmacokinetic study with BUD in children indicated that the risk of systemic side effects with this drug is low, since it was rapidly metabolized so that serum levels of BUD were always below the detection limit of the assay 4–8 hours after the inhalation of 1 mg BUD [11].

The asthma symptoms of many children are controlled by lower doses of inhaled GCS than those used in the present study. Systemic activity of lower doses of the two drugs should also be studied therefore, in order to define more accurately at which dose a significant systemic effect or a difference between the two drugs in systemic effect can be detected.

Conclusion

High dose inhaled therapy with BDP results in significantly lower urine cortisol excretion than high dose inhaled therapy with BUD in children with asthma; the difference being more pronounced in children treated with 1000 and 1200 μg GCS per day

than in children treated with 800 μg per day. The long term clinical significance of this has yet to be elucidated.

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RÉSUMÉ: 31 enfants asthmatiques ont été traités par inhalations de beclomethasone et de budesonide au cours d'une étude randomisée avec permutation croisée durant 2 × 6 semaines. L'excrétion de cortisol libre dans deux échantillons d'urines de 24 h, collectés à la fin de chaque période de traitement, s'est avéré significativement plus élevée (moyenne = 76.3 nmol/jour) au cours du traitement au budesonide, que pendant le traitement à la beclomethasone (moyenne = 53.7 nmol/jour) ($p < 0.01$). La différence entre les deux médicaments s'est avérée plus marquée chez les 8 enfants qui ont reçu 1000 et 1200 μg/jour que chez les 22 enfants qui ont reçu 800 μg/jour. Quatre enfants ont eu une excrétion de cortisol inférieure à la limite normale au cours du traitement par la beclomethasone. Ceci a été observé chez un enfant au cours du traitement au budesonide. Le résultat n'a pas été influencé par l'âge de l'enfant. La signification clinique à long terme de ces observations doit encore être élucidée.