Systemic activity of inhaled corticosteroid treatment in asthmatic children: corticotrophin releasing hormone test

L Pescollerungg, G Radetti, E Gottardi, D G Peroni, A Pietrobelli, A L Boner

**Background:** A study was undertaken to assess the function of the hypothalamic-pituitary-adrenal axis (HPA) in a group of asthmatic children before and after treatment with inhaled corticosteroids.

**Methods:** Thirty prepupal children of mean (SD) age 6.7 (1.8) years were treated with inhaled corticosteroids. All children underwent a corticotrophin releasing hormone (CRH) test with evaluation of serum cortisol and adrenocorticotrophin hormone (ACTH) levels before and after 3 months of treatment. Twenty four hour urine samples were also collected to measure free cortisol (UFC) excretion.

**Results:** Subjects showed no difference between basal serum cortisol levels (mean change –18; 95% CI –41 to 5; p=0.118) and delta (peak minus basal) levels (mean change –13; 95% CI –38 to 12; p=0.308) before and after treatment, whereas the peak cortisol level (mean change –31; 95% CI –55 to –7; p=0.013) and area under the curve (AUC) (mean change –175; 95% CI –288 to –63; p=0.003) after CRH were significantly lower following treatment. Basal, peak and AUC ACTH were significantly lower after treatment (p<0.05, p=0.004 and p=0.003, respectively), while delta ACTH was similar before and after treatment [mean change –12; 95% CI –31 to –7; p=0.199]. No significant reduction in 24 hour UFC was observed after the treatment period (before 14.9 (7.1), after 15.0 (11.6); mean change 0.1, 95% CI –5.2 to 5.4; p=0.967). No correlation was found between UFC and any of the parameters of cortisol excretion following the CRH test, either before or after treatment.

**Conclusions:** These data suggest that, at the dosage and for the treatment period used, inhaled steroids do not seem to suppress the HPA axis in the majority of patients. The CRH test may be more sensitive than 24 hour UFC and morning plasma cortisol levels in evaluating systemic activity of inhaled corticosteroid treatment.

**METHODS**

**Patients:** Thirty two prepubertal children suffering from frequent episodic or persistent asthma who required maintenance treatment with ICS were studied. Sixteen received inhaled fluticasone propionate (FP) by a metered dose inhaler (MDI) and spacer (Aereochamber), 100 µg twice daily (50 µg per actuation), and 16 received budesonide (BUD), 200 µg twice daily by Turbohaler (200 µg per actuation). Two subjects in the FP group failed to present at the scheduled visits and did not complete the study. Data are therefore presented on 30 patients (14 treated with FP and 16 treated with BUD) of mean (SD) age 6.7 (1.8) years, a height standard deviation score of 0.45 (0.77), body mass index (BMI) of SDS –0.1 (0.98), and body surface area 1.05 (0.35). The children were supervised in the correct use of the devices according to the manufacturers’ recommendations. Each dose was given at 08.00 and 20.00 hours. No child had been treated with oral or nasal corticosteroids in the previous 6 months and none had received inhaled corticosteroids. None of the children suffered from enuresis.

**Study design**

The HPA axis was evaluated in all children at baseline and 12 weeks after treatment with ICS. After an overnight fast and...
after the first dose of ICS, a CRH test (1 µg/kg IV as bolus) was performed at 09.00 hours to assess serum cortisol and ACTH levels (samples drawn at the following times: –15, 0, 15, 30, 45, 60, 90, 120 minutes). Twenty four hour urine samples were collected at home on the previous day for UFC assessment. All samples were frozen at –20°C until assayed.

Cortisol was assayed with Immulite 2000 cortisol kit (DPC, Los Angeles, CA, USA) which has a sensitivity of 0.02 µg/ml with an intra-assay coefficient of variation (CV) of 7.2%. ACTH was assayed with the Immulite 2000 ACTH kit (DPC, Los Angeles, CA, USA) which has a sensitivity of 5 pg/ml with intra- and inter-assay CVs of 6.7 % and 8.2%, respectively. UFC excretion was measured with Immunotech cortisol kit (Mar- seille, France) which has a sensitivity of 0.36 µg/ml with intra- and inter-assay CVs of 3.5 % and 7.5%, respectively.

**Statistical analysis**

The aim of this study was to evaluate the behaviour of the basal and reserve activity of the HPA axis after treatment with ICS and not to compare the effect of different corticosteroids. We therefore evaluated all the patients together to study the relationship between basal morning serum cortisol levels, the response to the CRH test, and 24 hour UFC excretion. A sample size of 32 patients was planned to ensure a power of at least 75% for detecting a difference after treatment of more than half the standard deviation at the usual 5% level of significance. For each difference a two sided paired t test was applied and the mean change from baseline together with the significance. For each difference a two sided paired t test was applied and the mean change from baseline together with the significance.

**Table 1** Cortisol and ACTH response to corticotropin releasing hormone (CRH) stimulation before and after 3 months of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Mean (SD)</th>
<th>After Mean (SD)</th>
<th>After – before Mean (SD)</th>
<th>95% CI</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (ng/ml)</td>
<td>155 65 137</td>
<td>78 –18</td>
<td>–41 to 5</td>
<td>0.118</td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>259 57 238</td>
<td>58 –31</td>
<td>–55 to 7</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>114 59 101</td>
<td>53 –13</td>
<td>–38 to 12</td>
<td>0.308</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>1275 303 1100</td>
<td>327 –175</td>
<td>–288 to –63</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>ACTH (µg/ml)</td>
<td>41 43 27</td>
<td>22 –14</td>
<td>–27 to –0.4</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>88 51 62</td>
<td>35 –26</td>
<td>–43 to 9</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>47 44 35</td>
<td>32 –12</td>
<td>–31 to 7</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>298 159 221</td>
<td>93 –77</td>
<td>–124 to –29</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>UFC</td>
<td>14.9 7.1 15.0</td>
<td>11.6 0.1</td>
<td>–5.2 to 5.4</td>
<td>0.967</td>
<td></td>
</tr>
</tbody>
</table>

UFC=urinary free cortisol.

Values are mean (SD).

*Paired t test.

- Figure 1 Basal and peak cortisol response to corticotrophin releasing hormone (CRH) before and after treatment with inhaled corticosteroids.

After the 12 week treatment period four patients, two treated with FP and two with BUD, who had a normal response before treatment had an abnormally low peak serum cortisol level (168 and 170 ng/ml in the patients treated with FP, 165 and 161 ng/ml in the patients treated with BUD, normal value >180 ng/ml; fig 1). In these four children, however, the basal serum cortisol level was normal (68 and 120 ng/ml in FP treated patients, 97.8 and 113 ng/ml in BUD treated patients, normal value >50 ng/ml).

Basal (mean change –14, 95% CI –27 to –0.4, p=0.045), peak (mean change –26, 95% CI –43 to –9, p=0.004), and AUC (mean change –77, 95% CI –124 to 9, p=0.003) ACTH levels were significantly lower after treatment, while delta ACTH was similar before and after treatment (mean change –12, 95% CI –31 to 7, p=0.199; table 1). In three of the four patients with a subnormal peak cortisol response after ICS treatment, the peak ACTH levels were reduced even if they were within the range of our study population, whereas in one patient the ACTH levels showed no change after treatment.

- No significant reduction was observed in 24 hour UFC excretion (µg/24 hours) after treatment (14.9 (7.1) v 15.0 (11.6), normal range 2–27 µg/24 hours; mean change 0.1, 95% CI –5.2 to 5.4, p=0.967; table 1). In three of the four patients with a subnormal peak cortisol response there was also a reduction in mean 24 hour UFC excretion which was, however, within the observed range of our study population. Nonetheless, one patient showed no changes after treatment.
No correlation was found between UFC and any of the parameters of cortisol excretion following the CRH test, either before or after treatment with ICS.

**DISCUSSION**

Assessment of HPA axis function appears to be the most sensitive and easily measured parameter of the potential systemic side effects of ICS treatment. The clinical significance of slight alterations in the HPA axis is uncertain and, in most patients, the presence of suppressed endogenous cortisol is not clinically relevant in itself. However, it can be used as a surrogate marker for potential adverse effects in other tissues. Based on this, the aim of our study was to assess the function of the HPA axis in a group of corticosteroid-naive asthmatic children before and after treatment with ICS.

Two broad types of tests can be used to detect HPA axis function—namely, measurement of basal adrenocortical activity and the dynamic stimulation test to evaluate adrenocortical reserve. In our study the dynamic evaluation of the HPA axis seems to be more sensitive than basal serum cortisol levels and 24 hour UFC excretion in detecting the systemic effect of corticosteroid treatment. Following the CRH test, four of our children (two treated with FP and two with BUD) had an inadequate response which could not have been predicted by normal morning serum cortisol levels (fig 1). The CRH test enables suppression of pituitary ACTH secretion to be distinguished from the more direct action on the adrenal response to ACTH. The CRH test stimulates pituitary ACTH secretion and this, in turn, produces a cortisol signal from the adrenal gland. It has been suggested that this physiological stimulation by including pituitary assessment may be more sensitive at detecting systemic steroid induced effects than basal adrenal testing alone, particularly with low dose ICS treatment.

In our study the lower peak ACTH secretion after treatment suggests that the suppression is mainly at the HPA level. Even though there were trends for both cortisol and ACTH reduction after treatment in all the parameters measured (table 1), only some of these changes reached statistical significance, reflecting the variability of the measurements and the changes over time, in addition to the effects of ICS treatment. More patients would improve the statistical power and significance, reflecting the variability of the measurements (table 1), only some of these changes reached statistical significance, reflecting the variability of the measurements and the changes over time, in addition to the effects of ICS treatment. More patients would improve the statistical power and significance of our results. However, the trend in our results suggests that the CRH test provides a cortisol signal from the adrenal gland. It has been suggested that this physiological stimulation by including pituitary assessment may be more sensitive at detecting systemic steroid induced effects than basal adrenal testing alone, particularly with low dose ICS treatment.

In our patients there was no clinical evidence of adrenal suppression; however, the CRH test proved to be particularly sensitive to the systemic activity of ICS, especially with respect to the ACTH response. The CRH test is expensive but it is not associated with potential side effects observed with other dynamic tests, such as metyrapone and insulin-induced hypoglycaemia. Metyrapone induced dizziness and nausea, as well as hypoglycaemia, and cannot be used in paediatric studies. The ACTH test might be an alternative, but it only gives an indirect evaluation of the HPA axis and it has already been shown in adult patients to be less accurate than the CRH test. Furthermore, both the standard (250 µg) and low dose (1 µg) ACTH tests lack the sensitivity and specificity to diagnose ACTH deficiency compared with the metyrapone test in adults. Moreover, the ACTH test is contraindicated in allergic and asthmatic subjects because of occasional reports of severe anaphylaxis.

In conclusion, our results suggest that a thorough evaluation of adrenal function cannot be obtained simply by measuring basal serum cortisol concentrations and/or 24 hour UFC excretion. In studies evaluating the systemic effects of ICS, dynamic evaluation of the HPA axis is more appropriate and CRH should provide an alternative research tool in asthmatic children.

**ACKNOWLEDGEMENTS**

The authors thank Dr Stella Lucia Volpe (University of Massachusetts, Amherst, MA, USA), Dr Moonseong Heo (Cornell University, White Plains, NY, USA) and Dr Giovanni Visonà for their insightful comments.

**Authors’ affiliations**

L Pescodlerungg, G Radetti, E Gottardi, Department of Pediatrics, Regional Hospital of Bolzano, Italy

D R Peroni, A Pietrofesa, A L Boner, Pediatric Department, University of Verona, Istituto Pio XII Misurina, Italy

**REFERENCES**


No cure for the common cold

Previous studies of Echinacea have reported success varying from 10% to 50% in the treatment of colds. A few randomised trials have reported only a small effect in preventing colds.

In this randomised, double blind, placebo controlled study the authors report on the effect of 10 days of treatment with dried, encapsulated, whole plant Echinacea starting within 36 hours of onset of symptoms in 142 students reporting common colds (69 Echinacea, 73 placebo). Their primary objective was to measure the severity and duration of reported upper respiratory tract infections. They concluded that there was no statistical difference between the two groups. They do, however, believe this should not be the last word on the use of Echinacea in the treatment of colds because (1) they used whole plant mixture rather than extracts as reported in previous trials, (2) they studied a healthy population of students in whom the clinical effect would be small, and (3) the trial was of modest size and would have missed an effect of 5–10%. Furthermore, they did not confirm infection by serological testing or inflammatory markers and simply based it on reported symptoms. This raises doubt about the exact aetiology of the illness.

This is a well designed study which clearly shows that whole plant Echinacea has no significant clinical effect on the course and severity of the common cold, although it is unlikely that this will end discussion on this subject.

K Hattotuwa
Broomfield Hospital, Chelmsford, Essex;
Hattotuwa@aol.com
Systemic activity of inhaled corticosteroid treatment in asthmatic children: corticotrophin releasing hormone test
L Pescolnderungg, G Radetti, E Gottardi, D G Peroni, A Pietrobelli and A L Boner

Thorax 2003 58: 227-230
doi: 10.1136/thorax.58.3.227

Updated information and services can be found at:
http://thorax.bmj.com/content/58/3/227

These include:
References
This article cites 26 articles, 1 of which you can access for free at:
http://thorax.bmj.com/content/58/3/227#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Drugs: respiratory system (526)
Child health (843)
Asthma (1782)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/