CLINICAL STUDY

Requirement for age-specific peak cortisol responses to insulin-induced hypoglycaemia in children

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Abstract

Objective: Based on adult data, a peak cortisol response ≥ 500 nmol/l to insulin-induced hypoglycaemia constitutes a normal. Age-specific reference ranges for basal morning cortisol have been developed for clinical use in the paediatric population. Such reference ranges are not clearly established for peak cortisol responses to insulin-induced hypoglycaemia despite limited data suggesting an effect of age on peak cortisol. The aims of this study were to assess factors affecting the cortisol response to insulin-induced hypoglycaemia in children and to determine whether the peak cortisol response was related to age.

Design: The present study was a retrospective cohort study.

Methods: Retrospective analysis of children and adolescents aged ≤ 18 years undergoing the insulin tolerance test with adequate hypoglycaemia was undertaken. Patients with hypopituitarism or severe hypothalamic–pituitary–adrenal axis impairment (peak cortisol value <400 nmol/l) or using systemic glucocorticoids were excluded.

Results: Two hundred and twenty-three tests were analysed. Peak cortisol responses ≥ 500 nmol/l occurred in 183 (82%) tests. Age was negatively associated with peak cortisol responses (r = −0.15, P = 0.03). A peak cortisol response < 500 nmol/l was significantly less common in patients aged <12 years (9/97 (9%) vs 31/126 (25%); P = 0.004). In children aged <12 years, the median (5th–95th centiles) peak cortisol values were 610 (480–806) nmol/l compared with 574 (442–789) nmol/l in children aged ≥ 12 years (P < 0.004). Similarly, median cortisol increment was significantly higher in younger patients (301 nmol/l compared with 226 nmol/l (P = 0.0004)).

Conclusions: Use of a single peak cortisol threshold in children of all ages is not appropriate and will result in overdiagnosis of adrenal insufficiency in adolescents.

European Journal of Endocrinology 169 139–145

Introduction

The insulin tolerance test (ITT) is the gold standard for the evaluation of the hypothalamic–pituitary–adrenal (HPA) axis (1, 2) and is regarded as the optimum test for the pharmacological assessment of GH secretion in children (3). In contrast to the extensive published literature pertaining to the GH response following insulin-induced hypoglycaemia in children, comparatively few reports have considered the magnitude of the cortisol response. Furthermore, several of these studies have reported mean peak cortisol responses without reporting measures of variability, proposing reference ranges or considering factors that may enhance or impair the responses (4, 5, 6).

Ethical considerations preclude the establishment of normative data regarding the HPA axis response to the ITT in healthy children. Studies seeking to establish paediatric reference data have suggested that a peak cortisol response between 400 and 550 nmol/l (14.4–20 μg/dl) constitutes a normal response (7, 8). The magnitude of the stress response to major surgery in 20 adult subjects was established by Plumpton & Besser (1), who equated it to a peak cortisol response to the ITT of 550 nmol/l (20 μg/dl). More recently, this value has been revised downwards to 500 nmol/l (18 μg/dl) (9) and has been validated in healthy adults (10), correcting for the 20–30% positive bias associated with the older fluorometric assay (1). Extrapolation from adult data has resulted in many paediatric centres employing a reference range for peak cortisol responses to insulin-induced hypoglycaemia between 500 and 550 nmol/l for all children and adolescents regardless of age (1, 2, 10).

Age-specific reference ranges for a variety of hormone assays have been developed for clinical use in the paediatric population, including one for basal morning cortisol (11). Such reference ranges are not clearly established for peak cortisol responses to insulin-induced hypoglycaemia, however, despite evidence
from small studies that the HPA axis response to this stimulus in children may be influenced by age (7, 8, 12). A study of 44 children with short stature and normal GH status identified a more vigorous ACTH response in younger children and proposed a normal cortisol response of 400 nmol/l at 40 min or 450 nmol/l (16.2 µg/dl) at 60 min after insulin administration (7). More recently, Crofton et al. (8) have determined that the peak cortisol response is age-related with their older counterparts. Cortisol thresholds of 550 nmol/l (20 µg/dl) for children aged <10 years and 470 nmol/l (17 µg/dl) for older children and adolescents have been proposed; however, these reference ranges have not been externally validated and thus not widely adopted.

At our institution, we aimed to retrospectively evaluate factors affecting the cortisol response in a large cohort of children and adolescents undergoing the ITT and facilitate the establishment of reference data.

Subjects and methods

We performed a retrospective review of all ITTs undertaken over a 5-year period (January 2004–December 2009) at our institution, a tertiary paediatric endocrinology centre in the Irish Republic. Patient data collected from case notes included age, gender, anthropometric data, diagnosis and medication history including use of systemic, inhaled or topical corticosteroids.

Insulin tolerance test

All testing was done in accordance with a protocol approved by the Institutional Review Board. Patients visited the Endocrinology Department at 0900 h having fasted from midnight. Prepubertal males and females with a bone age >10 years had pre-test sex-hormone priming. Once informed consent was obtained, an i.v. cannula was inserted and samples were obtained for priming. Once informed consent was obtained, an i.v. the T was administered at a dose of 0.1 units/kg provided that analyser at bedside. Actrapid insulin (Novo Nordisk) 2300 STAT; YSI, Yellow Springs, OH, USA) glucose performed using the Yellow Springs Instrument (YSI sample). Real-time blood glucose measurements were with a bone age fasted from midnight. Prepubertal males and females visited the Endocrinology Department at 0900 h having approved by the Institutional Review Board. Patients all testing was done in accordance with a protocol

ITT and facilitate the establishment of reference data.

Table 1 Clinical characteristics of subjects aged below and above 12 years.

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;12 years (n=97)</th>
<th>Age ≥12 years (n=125)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>80</td>
<td>0.89</td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Pubertal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td>94</td>
<td>34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pubertal</td>
<td>3</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short stature</td>
<td>73 (75)</td>
<td>75 (60)</td>
<td>0.02</td>
</tr>
<tr>
<td>Intracranial pathology</td>
<td>21 (22)</td>
<td>27 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Oncology including BMT</td>
<td>3 (3)</td>
<td>24 (19)</td>
<td>0.003</td>
</tr>
<tr>
<td>GH (mU/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>50</td>
<td>64</td>
<td>0.65</td>
</tr>
<tr>
<td>10–20</td>
<td>27</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>20</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Median cortisol values (nmol/l)</td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Male</td>
<td>590</td>
<td>559</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>615</td>
<td>584</td>
<td></td>
</tr>
<tr>
<td>BMI SDS &gt; 85th centile</td>
<td>27 (28)</td>
<td>25 (20)</td>
<td>0.16</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>9</td>
<td>4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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insufficiency and three patients who were administered i.v. hydrocortisone during the ITT because of distressing symptoms (all three had a subsequent peak cortisol value > 500 nmol/l during the 1 μg ACTH stimulation test). Seven patients had chromosomal disorders or dysmorphic syndromes, four other patients were excluded because of failure to induce hypoglycaemia, two patients were on long-term prednisolone treatment and one patient was hypoglycaemic at baseline and thus blood samples were collected but no insulin was administered. All patients with a history of haematological malignancies or solid tumours were relapse free for a minimum of 2 years after treatment prior to testing and none of the patients who underwent bone marrow transplantation (BMT) required glucocorticoids for graft-vs-host disease. Among those who underwent BMT, of 18 patients, only three had a peak cortisol value < 500 nmol/l (464, 479 and 486 nmol/l).

### Laboratory measures

Hypoglycaemia was defined as a glucose nadir ≤ 2.2 mmol/l (3, 14) or a glucose value < 2.6 mmol/l, with a 50% reduction from baseline (3). Peak cortisol and GH values were defined as the maximum absolute concentration reached during the ITT, regardless of when it occurred. Absolute and partial GH deficiencies were defined by peak stimulated GH responses < 10 and 10–20 mU/l respectively (15). Adrenal insufficiency was defined as a peak stimulated cortisol response < 500 nmol/l (2). Both GH and cortisol responses were determined on-site by an immunochromiluminescence assay, Immulite 2000 (Siemens Healthcare Diagnostics, New York, NY, USA). For GH, the assay sensitivity was 0.1 mU/l with intra-assay and inter-assay coefficients of variation (CV) values for a low point of the standard curve 5.4 and 7.9% respectively. For cortisol, the assay sensitivity was 28 nmol/l and between-run CV were 9.4, 4.7 and 4.4% at 97, 479 and 816 nmol/l respectively, with an intra-assay CV of 7.2%.

### Statistical analysis

Data were entered into a Microsoft Excel (Microsoft Corporation) spreadsheet. Statistical analysis was carried out using StatsDirect version 2.7.2. (StatsDirect, Cheshire, UK). Data are presented as mean ± s.d. or median (5th–95th centiles). Categorical variables were compared using the χ² analysis. Non-parametric variables were compared using the Mann–Whitney U or Kruskal–Wallis test with Kendall’s rank τ coefficient or non-parametric linear regression utilised for correlations. Variables that were normally distributed were compared using the Z-test as required for the large sample size. A P value < 0.05 was considered statistically significant.

### Results

Two hundred and twenty-three studies were eligible for inclusion in the analysis, 140 (63%) of which were performed in males. The mean age of the patients was 12.3 ± 3.5 years, range 3.7–18.5 years. Partial and absolute GH deficiencies were diagnosed in 68 (31%) and 114 (51%) tests respectively. Indications for testing patients stratified by age are presented in Table 1.

The median (5th–95th centiles) peak cortisol value was 580 (450–793) nmol/l (20.9 (16.2–28.5) μg/dl). Eighteen (8%) patients had a peak cortisol response at T₀. The median (5th–95th centiles) cortisol increment was 254 (0–477) nmol/l (9.1 (0–17.2) μg/dl).

### Table 2 Analysis of test characteristics in individuals with cortisol thresholds above and below the pre-study 500 nmol/l threshold.

<table>
<thead>
<tr>
<th>Peak cortisol value (nmol/l)</th>
<th>&lt;500</th>
<th>&gt;500</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>13.8</td>
<td>12</td>
<td>0.009</td>
<td>-2.9 to -0.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>112</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median nadir glucose (nmol/l)</td>
<td>1.88</td>
<td>1.7</td>
<td>0.12</td>
<td>-0.2 to 0.02</td>
</tr>
<tr>
<td>Median rate of fall glucose levels (mmol/min)</td>
<td>0.12</td>
<td>0.13</td>
<td>0.69</td>
<td>-0.02 to 0.01</td>
</tr>
<tr>
<td>Hypoglycaemia &lt;2.2 mmol/l at two testing points</td>
<td>47%</td>
<td>22%</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Mean glucose rise 10 min after nadir (nmol/l)</td>
<td>1.56</td>
<td>1.8</td>
<td>0.8</td>
<td>-0.27 to 0.34</td>
</tr>
<tr>
<td>Median basal cortisol values (nmol/l)</td>
<td>216</td>
<td>327</td>
<td>0.0003</td>
<td>38 to 135</td>
</tr>
<tr>
<td>Median cortisol increment (nmol/l)</td>
<td>237</td>
<td>286</td>
<td>0.003</td>
<td>-111 to -24</td>
</tr>
<tr>
<td>Frequency of GH deficiency</td>
<td>82.5%</td>
<td>81.4%</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>BMI SDS &gt; 85th centile</td>
<td>6 (15%)</td>
<td>47 (26%)</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Distribution of cortisol values <500 nmol/l according to age and diagnostic category.

<table>
<thead>
<tr>
<th>Age &lt;12 years (n (%))</th>
<th>Age ≥12 years (n (%))</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stature</td>
<td>6 (8)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Intracranial pathophysiology</td>
<td>3 (14)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Oncology</td>
<td>0</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Including BMT</td>
<td>9 (9)</td>
<td>31 (25)</td>
</tr>
</tbody>
</table>

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A peak cortisol response >500 nmol/l occurred in 183 (82%) tests.

Factors potentially affecting the cortisol response are outlined in Table 2. Patients who achieved a normal peak cortisol response were younger (median 12 vs 13.8 years, \( P=0.009 \) (95% CI -2.9 to -0.5 years)). Age was negatively associated with the peak cortisol response (\( r=-0.15, \ P=0.03 \) (95% CI -0.28 to -0.01)). A peak cortisol response < 500 nmol/l was significantly less common in patients aged < 12 years compared with older patients (9/97 (9%) vs 31/126 (25%); \( P=0.004 \); Table 3).

There was a significant positive correlation between basal and peak cortisol values (\( r=0.55, \ P<0.0001 \) (95% CI 0.44 to 0.63)). There was no relationship between age and basal cortisol values; however, cortisol increment (\( \Delta \) cortisol) was negatively correlated with age (\( r=-0.16, \ P=0.015 \) (95% CI -0.29 to -0.03)). There was an inverse relationship between cortisol increment and basal cortisol values (\( r=-0.79, \ P<0.0001 \) (95% CI -0.84 to -0.73); Fig. 1A, B, C and D).

In children aged < 12 years, the median (5th–95th centiles) peak cortisol values were 610 (480–806) nmol/l (22 (17.3–29) mg/dl) compared with 574 (442–789) nmol/l (20.7 (15.4–28.4) mg/dl) in children aged > 12 years (\( P<0.004 \)). Similarly, cortisol increments (\( \Delta \) cortisol) were also significantly higher in younger patients (301 (0–477) nmol/l (10.8 (0–17.2) mg/dl) compared with 226 (0–530) nmol/l (8.1 (0–19.1) mg/dl) (\( P=0.0004 \)).

There was a non-significant trend towards higher median cortisol values in females compared with males (601 vs 569 nmol/l; \( P=0.053 \)). Furthermore, the median cortisol values were not significantly different in patients with a BMI SDS > 85th percentile compared with those with a BMI SDS below it (599 vs 579 nmol/l; \( P=0.26 \)). There was no significant difference in the frequency of suboptimal cortisol responses in those with GH deficiency on testing compared with those with a normal GH response (\( P=0.87 \)). The median peak cortisol values were similar in both the groups (572 vs 580 nmol/l). GH and cortisol responses by age and diagnostic category are outlined in Table 4.

Discussion

To date, this is the largest study to have examined factors influencing the cortisol response of children and adolescents to the ITT, the gold standard for investigating the HPA axis. Our study replicated the findings of Crofton et al. (8), who demonstrated an inverse relationship between age and peak cortisol responses in 54 children and adolescents following insulin-induced hypoglycaemia. A more vigorous cortisol response to the ITT has also been reported in children aged < 3 years, although the test is no longer carried
out in this age group (12). In a study of 44 GH-sufficient children, Petersen (7) had demonstrated a similar inverse relationship between age and ACTH response (but not cortisol response) at 40 min after insulin administration. The apparent lack of a relationship between age and cortisol response in the latter study may have been because the cortisol values had not peaked. Peak cortisol responses occurred at $T_{a60}$ in 66% of our cohort, in accordance with other studies (8), and peak cortisol responses at $T_{a35}$ after insulin administration occurred in only 13%. In addition, a lack of relationship between ACTH and cortisol was also demonstrated, in accordance with other small studies (16, 17). It has been proposed that a small sample size and the assumption that the relationship between ACTH and cortisol is linear rather than logarithmic may be responsible for such an observation (18). It has also been reported that the response to exogenous ACTH in childhood varies with age (19, 20, 21, 22) and pubertal status (19); however, in some of these studies, ACTH was not dosed by body surface area and thus a relatively larger dose in younger children was a possible confounding factor (19, 21, 22).

Our data also suggest that the cortisol response to the ITT is influenced by age and that the use of a single age threshold of 500 nmol/l (a value extrapolated from adult practice) across the entire paediatric age group is inappropriate. Using this reference range, one in four adolescents will fail the test. Based on the Immulite assay, our data suggest cortisol limits of 480 and 440 nmol/l for adolescents will fail the test. Based on the Immulite assay, our data suggest cortisol limits of 480 and 440 nmol/l for children aged below and above 12 years respectively. The apparent lack of a relationship between age and cortisol response in the latter study may have been because the cortisol values had not peaked. Peak cortisol responses occurred at $T_{a60}$ in 66% of our cohort, in accordance with other studies (8), and peak cortisol responses at $T_{a35}$ after insulin administration occurred in only 13%. In addition, a lack of relationship between ACTH and cortisol was also demonstrated, in accordance with other small studies (16, 17). It has been proposed that a small sample size and the assumption that the relationship between ACTH and cortisol is linear rather than logarithmic may be responsible for such an observation (18). It has also been reported that the response to exogenous ACTH in childhood varies with age (19, 20, 21, 22) and pubertal status (19); however, in some of these studies, ACTH was not dosed by body surface area and thus a relatively larger dose in younger children was a possible confounding factor (19, 21, 22).

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Lashansky et al. (19) established normative data for adrenal steroidogenesis in a healthy paediatric population before and after 250 μg ACTH stimulation. A decline in cortisol levels was noted in early to mid-puberty (Tanner 2–3) in both sexes before the levels rose again in late puberty (Tanner 4–5). Post-stimulation cortisol levels were all $>497$ nmol/l in late puberty; however, levels as low as 414 nmol/l in males and 441 nmol/l in females were observed in the early-puberty group, following what is considered a supraphysiological stimulus based on the ACTH levels generated (26). It is, therefore, not surprising, considering that ACTH levels generated during the ITT are lower than those generated following a 1 μg ACTH test (26), that a significant proportion of our cohort aged $>12$ years (25%) had a peak cortisol response between 400 and 500 nmol/l. The findings of our study have implications not only for the ITT as the gold standard investigation but also for the more widely used low-dose ACTH stimulation test. Some authors claim that the low-dose ACTH stimulation test is equivalent in sensitivity to the ITT in terms of assessing adequacy of the stress response in adults. Previous studies in children have disputed this, however (27–29), and suggested that higher cortisol thresholds may be necessary for the low-dose ACTH stimulation test compared with the ITT. In light of the findings of our study, the effects of age will also have to be taken into account in calculating appropriate thresholds for the low-dose ACTH stimulation test in future studies involving children and adolescents.

Crofton et al. (8), however, found no difference in stimulated cortisol responses between pubertal and prepubertal subjects aged $>10$ years in a study that, as ours, included sex-steroid priming. The downward trend in peak cortisol responses in adolescence observed in our study could not be ascribed to confounding factors such as underlying diagnosis as the trend was observed across all three categories of patients tested and there was no significant difference in cortisol values between categories of patients aged below and above 12 years. Factors that have been demonstrated previously to affect cortisol values including gender, BMI and inhaled corticosteroid use did not influence the downward trend in peak cortisol responses in adolescence. Sexual dimorphism has been demonstrated...
Previously with respect to cortisol production and metabolism in adolescents (30) and older adults (31, 32). In our cohort, there was a non-significant tendency towards higher stimulated cortisol responses in females. With respect to BMI, cortisol production rate increases with increasing BMI, as does cortisol clearance. In addition, corticosteroid-binding globulin levels are lower; however, this does not always appear to manifest as increased free cortisol levels (33). Consequently, there was no difference in peak cortisol responses in subjects with a BMI SDS > 85th centile within our cohort.

We found a similar downward trend in peak cortisol responses in early adolescence as Crofton et al. had found; however, our suggested cortisol thresholds differed. One possible explanation for this discrepancy includes a difference in cortisol assay technique, which has been a major factor underpinning the variation in the reported reference ranges in many publications (34).

Possible limitations of our study include the fact that many centres have ceased to use the ITT for the investigation of the HPA axis due to apprehension regarding the safety of the procedure, particularly in young children. One might argue, however, that the demonstration of an effect of age on peak cortisol responses in our study merits further exploration among other tests of HPA axis function. The second limitation is that more than 80% of our study cohort had evidence of GH deficiency on testing. Owing to the aforementioned safety concerns, many centres only perform the test in children with a high pre-test probability of an abnormal result, and hence our results are applicable in this setting. We highlighted previously that ethical considerations preclude the establishment of normative data including a difference in cortisol assay technique, which has been a major factor underpinning the variation in the reported reference ranges in many publications (34).

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Conclusions

Our study identified significant age-related differences in the cortisol response to insulin-induced hypoglycaemia in children and adolescents and suggested that the use of a single stimulated cortisol threshold across the entire paediatric age range is inappropriate. This finding is supported by data from a number of smaller paediatric studies. Owing to the considerable variation that may occur in cortisol values between different assays, establishment of age-related thresholds for different assay techniques is mandatory and will avoid incorrect overdiagnosis of adrenal insufficiency.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 27 January 2013
Revised version received 4 May 2013
Accepted 14 May 2013

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