Oral dexamethasone administration: new pharmacological test for the assessment of growth hormone secretion

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Acute intravenous (iv) dexamethasone administration has been described recently as a new test for the diagnosis of growth hormone (GH) deficiency. In the present study, a new protocol of dexamethasone administration was evaluated. Twelve normal adults and 18 normal prepubertal children were studied. The dexamethasone iv test was performed in six adults at a dose of 4 mg and 12 children at a dose of 2 mg/m². Blood samples were collected 15 min before, at time zero and every 15 or 30 min during 5 h, resulting in a total of 16 samples. In the remaining six adults and six children, 8 and 4 mg, respectively, of dexamethasone were administered orally at the subject’s home, and blood sampling started 90 min later when they arrived at the hospital. Plasma GH was measured by radioimmunoassay. The dexamethasone-induced GH response (mean ± sxm, μg/l) to the iv or oral protocol did not differ in either the adults (iv 8.2 ± 2.1; oral 8.0 ± 1.6) or the children (iv 14.9 ± 1.3; oral 13.6 ± 1.8). It is concluded that the simpler protocol of acute oral dexamethasone administration hereby presented can be a safe and suitable test of GH secretion.

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Pharmacological tests are required to confirm the evaluation of growth hormone (GH)-deficient states. Many different tests have been described for this purpose (for a review, see Refs 1 and 2), but no single test can be considered as gold standard or complete enough to provide adequate information. Some of them can be hazardous or not exempt from risk (3), and the use of the specific stimulus GHRH is not helpful for the accurate diagnosis of the majority of GH deficiencies (4, 5). On the other hand, the significance of spontaneous GH levels for the diagnosis of GH insufficiency remains unclear (6).

We have shown recently that acute intravenous (iv) dexamethasone administration can be a suitable and safe test in the diagnostic armamentaria of GH secretory disorders (7–9). However, the performance of the dexamethasone test, as we have reported previously, can be considered too long (up to 5 h) and results in a large number of blood samples to be collected and processed (16 samples).

The aim of the present study was to evaluate the usefulness and reliability of a new, shorter and easier way to perform the dexamethasone test, maintaining its characteristics of safety and efficiency while increasing practicability.

Subjects and methods

Twelve normal male volunteers, aged 22 years, were studied after giving informed consent. They led normal lifestyles, were taking no medication and were within 10% of their ideal body weight. Six of them were tested with the intravenous dexamethasone test and the other six undertook the oral protocol.

A total of 18 normal prepubertal children (11 male and seven female, mean age 9.0 ± 2.4 years, mean ± sd) also were included in the study after receiving parental informed consent. The children were referred to the Paediatric Endocrine Clinic for evaluation of growth and were found to be normal. Approval for this study was obtained from the Hospital Ethic Committee for Clinical Research. All of them had normal height (mean ± sd: -1.1 ± 0.7 sd score) measured with a wall Harpenden stadiometer, and normal height velocity (mean ± sd: -0.5 ± 1.0 sd score) calculated over a period of at least 6 months. In all cases, weight was within 20% of ideal body weight. Bone age, estimated by the Greulich & Pyle Atlas, was according to chronological age (mean ± sd: 8.7 ± 1.8 years). They had normal response to classical pharmacological GH stimulation tests: oral clonidine (0.150 mg), insulin hypoglycaemia (0.1 IU/kg body wt of iv regular insulin) or GHRH (1.5 μg/kg body wt GHRH(1–29) as an iv bolus). The only side effect observed was drowsiness after the clonidine test and the known signs of hypoglycaemia. In addition to at least one of the classical tests performed, 12 of the children (eight male and four female) underwent the iv dexamethasone test.
while the remaining six (three male and three female) were submitted to the oral dexamethasone test.

The dexamethasone iv test was carried out as described previously (10). In brief, the test started at 09.00 h after an overnight fast and habituation to the hospital setting. With the subject recumbent, a butterfly needle was placed in a forearm vein and kept patent with saline-heparin solution. At time zero, dexamethasone (Fortecortin, Merck, Spain) was given as an iv bolus at a dose of 4 mg. Blood samples were taken 15 min before, at time zero, every 30 min during the first 2 h, every 15 min during the third and fourth hours and every 30 min during the last hour. Thus, a total of 16 samples were obtained during 5 h after dexamethasone administration.

In this new oral protocol, dexamethasone was given between 07.00 and 07.30 h at the subject’s home at a dose of 8 mg in normal adults and 4 mg in children. Sample collection started 90 min after the dose intake when the subject arrived at the hospital and then every 15 minutes for 2 h, the total time spent at the hospital being 2.5 h and the number of samples nine. No significant side effects were recorded during either iv or oral administration.

Human GH was measured in duplicate by commercial RIA kits (Diagnostic Products Co., CA). The sensitivity of the assay was 1 µg/l. Levels below the sensitivity of the assay were assigned half of the detection limit value (0.5 µg/l). Within-assay coefficients of variation were 4.9% and 3.7% at serum GH concentrations of 3.6 µg/l and 19.7 µg/l (N = 18), respectively. Between-assay coefficients of variation were 6.2%, 4.3% and 4.5% for GH concentrations of 3.1, 7.9 and 18.2 µg/l, respectively (N = 30).

Area under the secretory curve (AUC) was calculated by a trapezoidal method, adjusted for hour of test duration and expressed as µg/l × h. In the case of iv dexamethasone administration, only the period between 90 and 240 min (the period of oral test) was considered. Statistical analysis was performed by the non-parametric Mann–Whitney test for unpaired data. The level of significance was set at p < 0.05. Results are expressed as mean ± SEM.

Results

Normal adults

In the normal subjects, intravenous dexamethasone elicited a clear GH discharge over the basal values (peak 8.2 ± 2.1 µg/l; AUC 256 ± 70). Acute oral administration of dexamethasone led to a significant GH release over the basal value (peak 8.0 ± 1.6 µg/l; AUC 255 ± 63). No significant differences in either GH peak or AUC levels were observed between iv or oral tests.

The characteristic pattern and kinetics of GH response to dexamethasone are illustrated in Fig. 1. Plasma GH values were similar in both groups at 90 min (iv 0.8 ± 0.3; oral 1.9 ± 0.9) when the first blood sample of the oral test was obtained, and tended to return to baseline levels 4 h after the stimulus. All the maximal responses were produced within the interval of 120–240 min after administration of the drug.

Normal children

All the children had normal responses to the classical GH tests performed, according to our own reference values (data not shown). Table 1 summarizes the results for each stimulus.

Intravenously administered dexamethasone produced a clear GH release in normal children (peak 14.9 ± 1.3 µg/l; AUC 323 ± 22) that was not signifi-
Table 1. Plasma growth hormone response to pharmacological tests in normal prepubertal children.

<table>
<thead>
<tr>
<th>Test</th>
<th>Peak (µg/l)</th>
<th>AUC (µg/l x h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Range</td>
</tr>
<tr>
<td>Clonidine</td>
<td>17.2 ± 1.4</td>
<td>9.7–21.6</td>
</tr>
<tr>
<td>Insulin hypoglycaemia</td>
<td>9.3 ± 1.1</td>
<td>6.9–12.1</td>
</tr>
<tr>
<td>GHRH</td>
<td>39.6 ± 12.1</td>
<td>9.1–90.8</td>
</tr>
<tr>
<td>l.v. dexamethasone</td>
<td>14.9 ± 1.3</td>
<td>9.8–22.3</td>
</tr>
<tr>
<td>Oral dexamethasone</td>
<td>13.6 ± 1.8</td>
<td>9.2–20.8</td>
</tr>
</tbody>
</table>

significantly different from that obtained by oral administration (peak 13.6 ± 1.8 µg/l; AUC 357 ± 106) (Fig. 2).

Plasma GH levels at 90 min were similar in both groups (iv 0.5 ± 0.0; oral 1.0 ± 0.3 µg/l). All the
dexamethasone-induced GH peaks were produced within 120–240 min.

The GH peaks after both iv and oral dexamethasone
tests were significantly higher (p < 0.05) than their respective values in adults, while no differences were found for the AUC.

Discussion

Growth delay is a common problem in paediatric patients. In the majority of them, short stature is due
to a variety of causes, mainly familial short stature,
constitutional growth delay, specific syndromes or, less
frequently, GH insufficiency. Nowadays, the unlimited
availability of biosynthetic recombinant GH has ensured
the adequate supply for all patients with GH
insufficiency. However, the accurate identification of
patients who would benefit from treatment with GH is
often difficult and must be accomplished carefully to
avoid unnecessary therapies.

In addition to the essential clinical study, comprising
at least the assessment of height, height velocity and
bone maturation, many different approaches have been
proposed and developed for the analytical evaluation of
GH deficiency. Spontaneous GH secretion, IGF and
binding protein evaluation may help in some instances
to identify GH-deficient patients. Nevertheless, provoc-
cative tests also are required to complete the clinical
evaluation of somatotroph function, and the diagnosis
of GH deficiency is still based, in most situations, on a
subnormal GH release after two or more pharmacological
stimuli.

Although pharmacological GH stimulation tests are
widely used, they can be unpleasant, not exempt from risk or not helpful for the diagnosis of GH insufficiency.
In fact, oral clonidine administration is a simple and safe
test, routinely performed at many Centres as a screening
test. However, the administration of this α-adrenergic agonist in children produces discomfort and drowsiness (11) that interferes with routine activities. Insulin hypoglycaemia has become the most common test for GH secretion, but it has been reported recently that hypoglycaemia or its mismanagement may induce severe complications (3). It can be recommended, therefore, that paediatricians should be more cautious in requiring the insulin test. Finally, it is well known that a high percentage of idiopathic GH-
deficient patients have normal GH response to a single
GHRH injection (12), resulting in an overlap between
normal and deficient patients. Thus, a normal response

Fig. 2. Growth hormone response (mean ± SEM) to dexamethasone stimulation test (DEX) in normal children: (A) response curves. (B) mean peak and area under the curve. Open circles and bars: iv route; solid circles and bars: oral route.
to GHRH does not exclude the presence of a GH-deficient secretion (4, 5).

The surprising finding that acute administration of corticoids was able to induce a potent GH response (7, 13) led us to the evaluation of dexamethasone, a potent and well-known synthetic glucocorticoid, as a new stimulus for pharmacological GH testing. In latter years, the dexamethasone test has become well established for the assessment of GH secretion in different pathological situations, such as GH deficiency (8, 10), obesity (14, 15) or patients affected by pituitary tumours (9). Although the usefulness and safety of the iv administration was demonstrated in adults and children, the test has the disadvantage of being of long duration and comprising the collection of a large number of samples. In order to make it more convenient, we can take advantage of two findings: first, all the peaks take place between 2 and 4 h after the stimulus. This delayed dexamethasone-induced GH release is the most characteristic pattern of the test and clearly different from the other stimuli, which usually have a more precocious discharge. The second finding relies on the equal potency of the oral route. In fact, we have reported previously that orally administered dexamethasone induced a GH increase similar to that after the iv pathway in adult subjects (7), although a direct comparison between both routes was not performed systematically. This is the first study of the oral dexamethasone test in children. In order to improve the procedure of the test in terms of simplicity without decreasing efficiency, for the present study we designed a new protocol comprising the intake of dexamethasone at the patient’s home before moving to hospital. Thus, the time at the hospital was diminished significantly, along with the total number of GH samples obtained, thus maintaining the efficiency of the test. In order to avoid undesirable premature GH secretion, the need to minimize physical exercise prior to the test must be emphasized.

The fact that mean GH peak was significantly lower in adults than in children is noteworthy. This finding might reflect an age-related decrease in GH response to dexamethasone, as has been reported for other tests (16).

In comparison with the other stimuli administered (Table 1), dexamethasone appears to be as potent a GH secretagogue as clonidine and even more so than insulin-induced hypoglycaemia. On the other hand, GHRH is revealed as the most potent GH stimulus, in agreement with several previous reports. We would like to emphasize that the dexamethasone test, like other methods of investigation of GH reserve, cannot be exempt from false results and deserves further, more extensive studies.

In conclusion, we have compared the effect of iv versus oral dexamethasone administration on GH secretion in normal adults and children. Our data confirm that the dexamethasone test has an adequate GH-releasing potency in both adults and children, and can be a good alternative among GH-secretory pharmacological tests. Furthermore, the new oral protocol evaluated in the present study offers the advantage of a shorter hospital stay and fewer samples to be processed, without affecting its efficiency. In summary, this test can be a new suitable test for GH secretion.

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