CLINICAL STUDY

Diagnosis of growth hormone deficiency in adults by testing with GHRP-6 alone or in combination with GHRH: comparison with the insulin tolerance test

Stephan Petersenn, Roman Jung¹ and Frank U BeilDepartment of Medicine and ¹Department of Clinical Chemistry, University Clinic Eppendorf, University of Hamburg, 20251 Hamburg, Germany

(Correspondence should be addressed to S Petersenn, Division of Endocrinology, Medical Center, University of Essen, Hufelandstr. 55, 45122 Essen, Germany; Email: stephan.petersenn@uni-essen.de)

Abstract

Objective: The diagnosis of GH deficiency in adults should be made using provocative testing of GH secretion. The insulin tolerance test (ITT) is recommended as the gold standard investigation. Because of the risk of serious complications, patients with epilepsy or known ischemic heart disease should not undergo this test. GHRP-6 is a synthetic hexapeptide that releases GH by binding to specific hypothalamic and pituitary receptors. We assessed the diagnostic capability of GH stimulation by GHRP-6 alone or in combination with GHRH in comparison to the results of an ITT.

Design: Twenty patients underwent an ITT for suspected pituitary or adrenal disease. Either GHRP-6 (1 µg/kg) alone, or GHRP-6 in combination with GHRH (1 µg/kg) were administered on different days. Blood samples were obtained during a subsequent 90-min period for measurement of GH.

Results: Ten patients had a GH peak response of less than 3 µg/l during ITT and were considered growth hormone deficient (GHD). The GH mean peak ($\pm$ S.E.M., range) in this group was 0.7 µg/l ($\pm$ 0.3, 0.1–2.9) compared with 14.5 µg/l ($\pm$ 3.5, 3.8–40.8) in the group of patients with a GH peak response of more than 3 µg/l (growth hormone sufficient (GS)). For the GHRP-6 test, the GH mean peak was 1.3 µg/l ($\pm$ 0.6, 0.1–6.7) in the GHD group versus 25.7 µg/l ($\pm$ 5.5, 7.7–54.2) in the GS group. After GHRP-6 + GHRH, the GH mean peaks were 4.0 µg/l ($\pm$ 1.3, 0.2–11.9) versus 54.7 µg/l ($\pm$ 11.1, 13.9–136.0) respectively. During administration of GHRP-6, the only side effects observed were flush symptoms.

Conclusions: Peak GH levels below 7 µg/l for the GHRP-6 test and below 13 µg/l for the combined GHRP-6 + GHRH test identified all patients with GH deficiency correctly as defined by ITT. The results suggest that testing with GHRP-6 or GHRP-6 + GHRH is as sensitive and specific as an ITT for the diagnosis of adult GH deficiency.

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Introduction

Growth hormone (GH) deficiency in adults is thought to result in abnormalities of body composition, reduced physical performance, impaired psychological well-being, and premature mortality (1). Replacement of GH may improve impaired health in such patients. Therefore, patients with evidence of hypothalamic–pituitary disease, subjects who have received cranial irradiation, or patients with childhood onset of GH deficiency should be evaluated for GH deficiency (2). The diagnosis of GH deficiency is established by provocative testing. The insulin tolerance test (ITT) has been indicated as the test of choice. Severe GH deficiency has been defined by a GH peak of less than the arbitrary cut-off of 3 µg/l (2). The test is contraindicated in patients with electrocardiographic evidence or history

of ischemic heart disease, or in patients with seizure disorders. It should only be performed in experienced endocrine units and requires careful supervision that makes it very expensive and inappropriate as a screening procedure. Whereas adult patients with hypothalamic disease and one or more additional pituitary hormone deficits require only one provocative test of GH secretion, it is recommended that a second biochemical test of GH status is performed to establish the diagnosis of isolated GH deficiency (2). For such patients and for patients with contraindications to the ITT it seems necessary to establish other stimulatory tests with appropriate cut-offs.

GH secretion by the anterior pituitary is under complex control. Small synthetic molecules termed GH secretagogues (GHS) act on the pituitary and the hypothalamus to stimulate and amplify pulsatile GH release

(3). These compounds appear to mimic a putative endogenous ligand which activates a receptor distinct from that of GH-releasing hormone (GHRH) and somatostatin (4). The function of this receptor is probably critical for regulation of normal GH secretion. Analogs studied so far include GHRP-2, GHRP-6, Hexarelin and MK-0677 (5). An endogenous specific ligand of 28 amino acids has recently been purified from rat stomach; it has been termed 'ghrelin' (6). GHS may offer practical diagnostic and therapeutic value in humans. They show potent and reproducible GH-releasing activity, release more GH than GHRH, and truly synergizes with GHRH (7). We compared GH provocation by GHRP-6 alone or by GHRP-6 plus GHRH with an ITT for the diagnosis of GH deficiency in adults.

Subjects and methods

Patients

Twenty patients (11 male and 9 women, aged 19–66 years, BMI 19.8–33.9 kg/m²) underwent an ITT at our department because of suspected pituitary or adrenal disease (Table 1). Thirteen patients had a history of tumors in the pituitary area (five non-functioning adenomas, three corticotrophic adenomas, one prolactinoma, two pituitary cysts, one meningioma, one craniopharyngeoma), and four patients had a history of pituitary hormone deficiency (two congenital, one traumatic, one diabetes insipidus). Two patients had a

diagnosis of short stature, and one patient was operated on for an adrenal mass. Some of these patients had received previous treatment by operation or radiation. All patients with pituitary insufficiencies other than GH had been receiving optimal replacement therapy for at least 3 months. No patients had received recombinant GH for at least 1 year before testing.

The local ethics committee approved the study protocol, and all subjects gave their informed written consent to participate in the study.

Methods

Patients underwent an ITT by injection of 0.1–0.15 IU/kg of regular insulin (Actrapid Novo Nordisk, Mainz, Germany) to achieve blood glucose levels below 40 mg/l and until symptoms of hypoglycemia developed. All patients underwent testing with GHRP-6 (CLINALFA AG, Läufelfingen, Switzerland; 1 µg/kg; i.v. at 0 min) alone and in combination with GHRH (Ferring GmbH, Kiel, Germany; 1 µg/kg; i.v. at 0 min). All tests were performed in the morning after an overnight fast, at least 1 day apart. Blood samples for GH assay were taken at 0, 15, 30, 45, 60 and 90 min. Basal IGF-I levels were determined in all patients. Corticotrophic function was assessed by ITT, gonadotrophic and thyrotrophic functions were determined by provocation with gonadotrophin-releasing hormone (GnRH) and thyrotrophin-releasing hormone

Table 1 Clinical characteristics of 20 patients with suspicion of pituitary or adrenal disease tested by ITT. Sufficient (s) or insufficient (i) pituitary hormone function is indicated, as determined by provocation tests. IGF-I values at the time of testing are shown.

No	Sex	Age	BMI	Diagnosis	GH	Cortisol	TSH	LH/FSH	IGF-I (µg/l)
1	m	31	20.8	Cushing → OP	s	i	s	s	153
2	f	66	20.1	NFA → OP	s	s	s	s	79
3	f	19	19.8	Diabetes insipidus	s	s	s	s	451
4	f	33	20.3	Adrenal adenoma → OP	s	s	s	s	316
5	m	52	27.7	NFA	s	s	s	s	359
6	m	55	27.8	Prolactinoma	s	s	s	i	290
7	m	50	25.3	Cyst	s	s	s	s	169
8	f	43	23.1	NFA	s	s	s	s	43
9	m	27	19.9	Short stature	s	s	s	s	247
10	m	57	25.6	Short stature	s	s	s	s	203
	6/4	43	23.0		0/10	1/10	0/10	1/10	231
11	m	32	23.2	Trauma	i	i	i	i	15
12	f	41	26.2	Congenital PHD	i	i	i	i	16
13	f	64	25.1	Cushing → radiation	i	s	i	i	74
14	m	57	24.2	NFA → OP	i	i	i	i	86
15	f	60	33.4	NFA → OP	i	i	i	i	36
16	f	37	33.9	Cyst → OP	i	i	i	i	15
17	m	55	27.4	Craniopharyngioma	i	s	i	i	116
18	m	27	24.9	Congenital PHD	i	s	s	i	18
19	f	50	28.3	Meningioma	i	s	s	s	131
20	m	47	27.7	Cushing → OP + radiation	i	s	i	i	145
	5/5	47	27.4		10/10	5/10	8/10	9/10	65

BMI, body mass index; TSH, thyrotropin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; OP, operation; NFA, non-functioning adenoma; PHD, partial hormone deficiency.

(TRH) respectively. After centrifugation, plasma samples were stored at -20°C until analysis.

Serum GH levels (μg per litre) were assayed at each time point by RIA (CIS bio international, Gif-Sure-Yvette Cedex, France). The lower detection limit was assessed to be $0.04\text{ }\mu\text{g/l}$. Intra-assay variations as coefficient of variation for various GH values were 2.4% ($3.46\text{ }\mu\text{g/l}$), 2.8% ($7.3\text{ }\mu\text{g/l}$) and 2.3% ($47.4\text{ }\mu\text{g/l}$). Inter-assay variations were 4.2% ($3.3\text{ }\mu\text{g/l}$), 3.2% ($7.1\text{ }\mu\text{g/l}$) and 4.0% ($45.5\text{ }\mu\text{g/l}$). Normal values of spontaneous GH secretion were obtained by the manufacturer of the assay from presumed healthy adult subjects of both sexes. All values were in the $0\text{--}10\text{ }\mu\text{g/l}$ range, and 93.8% were below $7\text{ }\mu\text{g/l}$. Basal serum insulin-like growth factor-I (IGF-I) levels (μg per litre) were determined by chemiluminescence immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The analytical sensitivity of the assay was determined as $6\text{ }\mu\text{g/l}$. Intra-assay variations as coefficient of variation for various IGF-I values were 4.8% ($63\text{ }\mu\text{g/l}$), 5.2% ($208\text{ }\mu\text{g/l}$) and 4.4% ($766\text{ }\mu\text{g/l}$). Inter-assay variations were 7.1% ($62\text{ }\mu\text{g/l}$), 5.7% ($215\text{ }\mu\text{g/l}$) and 7.4% ($811\text{ }\mu\text{g/l}$). Normal values for adult IGF-I values in our laboratory were $182\text{--}780\text{ }\mu\text{g/l}$ (16–24 years), $114\text{--}492\text{ }\mu\text{g/l}$ (25–39 years), $90\text{--}360\text{ }\mu\text{g/l}$ (40–54 years) and $71\text{--}290\text{ }\mu\text{g/l}$ (55+ years), as provided by the manufacturer.

Area under the curve (AUC) values were calculated by use of GraphPad Prism 3.0 software. Results (mean $\pm$ S.E.M.) are expressed as absolute values for GH as well as for IGF-I. Statistical analysis was performed by Mann–Whitney test where appropriate. GraphPad Prism 3.0 software was used for analysis of correlation.

Results

ITT

Twenty patients with suspected pituitary or adrenal disease were included in this study. Provocation by hypoglycemia induced a marked GH release in ten subjects with a GH peak response of more than $3\text{ }\mu\text{g/l}$ (growth hormone sufficient (GS)) (Fig. 1a). Ten patients with a GH peak response of less than $3\text{ }\mu\text{g/l}$ were considered GH deficient (GHD) following the recommendations of a recent consensus statement (2). Elevated mean GH levels were observed 30–90 min after administration of insulin for the GS subjects as expected, whereas mean GH levels remained virtually unchanged at all time points for the GHD patients (Fig. 2a). The GH mean peak ($\pm$ S.E.M., range) was $0.7\text{ }\mu\text{g/l}$ (± 0.3 , $0.1\text{--}2.9$) in GHD patients, significantly lower ($P < 0.0001$) as compared with $14.5\text{ }\mu\text{g/l}$ (± 3.5 , $3.8\text{--}40.8$) in GS subjects. Individual peak responses occurred at varying times (three patients after 30 min, five patients after 45 min, ten patients after 60 min, two patients after 90 min).

Calculation of the AUC revealed an overlap between the GHD and the GS group (Fig. 1b). In all GHD patients the AUC was $<200\text{ }\mu\text{g/l}$ per 90 min whereas in nine of ten GS subjects it was $>200\text{ }\mu\text{g/l}$ per 90 min. Choosing an arbitrary cut-off of $200\text{ }\mu\text{g/l}$ per 90 min to define GH deficiency, one subject defined as non-GHD using the GH peak data was classified as GHD. The mean AUC ($\pm$ S.E.M., range) was $36.1\text{ }\mu\text{g/l}$ per 90 min (± 16.4 , $3.6\text{--}155.0$) in the GHD group versus $713.4\text{ }\mu\text{g/l}$ per 90 min (± 167.5 , $91.3\text{--}1839.0$) in the GS group ($P < 0.0001$).

GHRP-6 test

GHRP-6 alone was found to be more potent in releasing GH than hypoglycemia (Fig. 2b). The results were grouped according to the classification by ITT peak

Figure 1 Analysis of GH (a) peak levels and (b) AUC. Individual values during ITT (squares), GHRP-6 test (triangles), and GHRP-6 + GHRH test (circles) are demonstrated. Patients were defined as GHD (closed symbols) or non-GHD (GS, open symbols) based on their GH peak response to hypoglycemia of $<3\text{ }\mu\text{g/l}$ or $>3\text{ }\mu\text{g/l}$.

Figure 2 GH levels during (a) ITT, (b) GHRP-6 test, and (c) GHRP-6+GHRH test. Results (mean $\pm$ S.E.M.) are shown for GHD (circles) or non-GHD subjects (GS, squares).

values. The GH mean peak ($\pm$ S.E.M., range) was 1.3 μ g/l ($\pm$ 0.6, 0.1–6.7) in the GHD group versus 25.7 μ g/l ($\pm$ 5.5, 7.7–54.2) in the GS group ($P < 0.0001$). Individual peaks occurred in 14 subjects at 15 min, and in six subjects at 30 min. The mean GH AUC ($\pm$ S.E.M., range) was 52.9 μ g/l per 90 min ($\pm$ 20.1, 5.2–177.1) in the GHD group versus 1102.7 μ g/l

per 90 min ($\pm$ 269.2, 243.6–2975.0) in the GS group ($P < 0.0001$).

There was a strong positive correlation between the GH peak responses during ITT and the GHRP-6 test (Fig. 3a, $r = 0.87$, $P < 0.0001$). Choosing an arbitrary cut-off of 7 μ g/l for the GH peak levels, there was 100% concordance in the diagnosis of GH deficiency by both tests for all our subjects (Fig. 1a). In addition, an AUC below 200 μ g/l per 90 min identified all patients with GH deficiency correctly as defined by GH peak response during ITT (Fig. 1b).

Figure 3 Individual GH peak levels during ITT in 20 subjects plotted against GH peaks during (a) GHRP-6 test and (b) GHRP-6+GHRH test. Symbols for patients with very low GH levels overlay each other.

GHRP-6 + GHRH test

Administration of GHRP-6 + GHRH caused a prompt release of GH (Fig. 2c). The GH mean peaks ($\pm$ S.E.M., range) were 4.0 μ g/l ($\pm$ 1.3, 0.2–11.9) in the GHD group versus 54.7 μ g/l ($\pm$ 11.1, 13.9–136.0) in the GS group ($P < 0.0001$). Individual peaks occurred in 17 subjects at 15 min, and in three subjects at 30 min. The mean AUC ($\pm$ S.E.M., range) was 190.6 μ g/l per 90 min ($\pm$ 61.4, 11.4–536.9) in the GHD group versus 2491.8 μ g/l per 90 min ($\pm$ 629.3, 578.0–7555.0) in the GS group ($P < 0.0001$).

As for the GHRP-6 test, there was a strong positive correlation between the GH peak responses during ITT and the GHRP-6 + GHRH test (Fig. 3b, $r = 0.88$, $P < 0.0001$). Peak GH levels below 13 μ g/l for the GHRP-6 + GHRH test identified all patients with GH deficiency as well as all patients with sufficient GH secretion correctly as defined by ITT (Fig. 1a). Choosing an arbitrary cut-off of 550 μ g/l per 90 min for the AUC, all patients defined as GHD by GH peak response during ITT are correctly classified (Fig. 1b).

Comparison to IGF-I

The IGF-I levels (mean $\pm$ S.E.M., range) in GHD patients (65.2 ± 16.4 , 15.0–145.0) were lower than those in GS subjects (231.0 ± 40.1 , 43.0–451.0) with some overlap between the two groups ($P < 0.01$). One subject with sufficient GH secretion had IGF-I levels below his normal age-related reference values. Five patients considered GHD by all provocation tests had normal age-related IGF-I values, although two of them had IGF-I values at the very lower end of the reference range.

There was a strong positive correlation between the GH peak responses and IGF-I levels for the GHRP-6 test ($r = 0.77$, $P < 0.0001$) as well as between GH peaks and IGF-I values for the GHRP-6 + GHRH test ($r = 0.82$, $P < 0.0001$). For comparison, the correlation between GH peaks during ITT and IGF-I levels was calculated to be 0.73 ($P < 0.001$). Similar correlations between AUC and IGF-I were found for the GHRP-6 test ($r = 0.78$, $P < 0.0001$) and for the GHRP-6 + GHRH test ($r = 0.82$, $P < 0.0001$).

Side effects

During ITT, clinical intervention was necessary in three subjects because of severe symptoms of hypoglycemia. However, after administration of GHRP-6 or GHRP-6 + GHRH, the only side effects observed consisted of mild flushing.

Discussion

The results of this study show that provocative tests using GHRP-6 alone or in combination with GHRH are reliable tools for the diagnosis of GH deficiency in

adults. Peak GH levels below 7 μ g/l for the GHRP-6 test and below 13 μ g/l for the combined GHRP-6 + GHRH test were successful in identifying all patients with GH deficiency correctly as defined by ITT. Thus, with appropriate cut-off values, these tests are as sensitive and specific as the ITT that is considered the gold standard.

The only other study of a single GHS test for diagnosis of GH deficiency in adults was performed by Korbonits *et al.* (8). These authors used a different GHS (Hexarelin, 2 μ g/kg) to investigate the GH response in 19 patients with possible pituitary disease. Seven patients were found to be severely GHD defined by ITT. For Hexarelin testing, the authors established a lower limit of the normal GH response of 13.8 μ g/l. Because of different substances and dosages, stimulated GH values cannot be compared with our own study. Six of their GHD patients had a GH response to Hexarelin below the limit, while the seventh patient was just above the borderline (14.7 μ g/l). All non-GHD subjects, as identified by ITT, were correctly classified by the Hexarelin test. Similar to our results with GHRP-6, a test using Hexarelin alone for provocation of GH release had a high sensitivity and specificity for the diagnosis of severe GH deficiency.

Most groups studied GHS combined with GHRH for the diagnosis of GH deficiency in adults. In a recent multicenter study, Popovic and co-workers (9) investigated 125 adult patients with organic pituitary disease by performing an ITT and by testing with GHRP-6 (1 μ g/kg) in combination with GHRH (1 μ g/kg). The mean GH peaks during ITT (GHD group: 0.5 μ g/l; GS group: 14.3 μ g/l) were lower than in our study (GHD group: 1.3 μ g/l; GS group: 25.7 μ g/l). In contrast, their results of the GHRP-6 + GHRH test (GHD group: 4.1 μ g/l; GS group: 59.2 μ g/l) were virtually identical to our study (GHD group: 4.0 μ g/l; GS group: 54.7 μ g/l). Therefore, whereas results of an ITT may depend on specific conditions in the endocrine unit resulting in various degrees of hypoglycemia, the GHRP-6 + GHRH test appears to be less prone to such variations. By ROC curve analysis, Popovic *et al.* identified a cut-off of 15 μ g/l for GH peaks as being the best threshold decision. Our own study suggests a cut-off of <13 μ g/l to identify GHD subjects. Although the study of Popovic *et al.* includes a larger number of patients, GH levels were measured in various centers using seven different GH assays. Different cut-off values may result from GH assay variations, indicating that each laboratory should establish its own criteria for normality of response using its own GH assay.

Some groups utilized GHS other than GHRP-6 in combination with GHRH for provocation of GH release. Gasperi and co-workers compared GH provocation by Hexarelin (0.25 μ g/kg) combined with GHRH (1 μ g/kg) with the results of an ITT in healthy subjects and 19 GHD patients (10). Analyzing the GHD patients, the authors found a mean GH peak of 2.6 μ g/l during

Hexarelin + GHRH testing. Normal GH peak response during Hexarelin + GHRH testing was defined by the first percentile limit established from healthy subjects. All GHD subjects but also some healthy subjects had GH peaks below 51.2 µg/l, which results in a sensitivity of 100% but somewhat lower specificity.

All subjects in our study had peak values either 15 min or 30 min after administration of GHRP-6 test or GHRP-6 + GHRH. In their larger study, Popovic *et al.* found only 24 subjects with GH peaks at 45 min or later. Apparently, peak values in these subjects were similar to values obtained at 30 min (9). Therefore, provocative tests using GHS may be limited to a maximum interval of 30 min without losing diagnostic information. The AUC was as good as GH peak values to classify GHD subjects but is more cumbersome to obtain and does not offer any diagnostic advantage, judged by the results of our study. Although IGF-I levels were lower in GHD patients compared with GS subjects, there was a significant overlap between the two groups. Five GHD subjects (50%) are falsely classified as GH sufficient by IGF-I values, and one GS subject (10%) is falsely classified as GHD. It has previously been demonstrated that circulating IGF-I levels do not provide a reliable marker of GH secretion in adults because they are greatly influenced by nutritional and metabolic status, IGF-I and IGF-binding protein-3 (IGFBP-3) being within the normal range in more than 60% of patients with GH deficiency (11, 12).

In summary, the results suggest that a test using GHRP-6 test or GHRP-6 + GHRH for provocation of GH release is as sensitive as an ITT for the diagnosis of adult GH deficiency. It remains to be seen if other GHS are as useful as diagnostic tools. Whereas most groups used GHS in combination with GHRH, we found a single GHS test as sensitive and specific. In contrast to the ITT, there are very few side effects and no obvious contraindications for such a test. It is generally recommended to generate normative values before a test is used for routine investigation. Cut-off limits should be established appropriate to that test. Therefore, further investigation of the GHRP-6 test and the GHRP-6 + GHRH test are necessary, before they may be considered to replace the ITT.

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