Growth hormone responses to oral glucose and intravenous thyrotropin-releasing hormone in acromegalic patients treated by slow-release lanreotide

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ABSTRACT. The aim of this study was to assess GH response to oral glucose tolerance test (OGTT) and TRH stimulation test in a group of 10 patients with active post-operative acromegaly before and after long-term slow-release (SR) lanreotide therapy (30 mg im every 10-14 days). Seven patients (2 males, 5 females, 29-71 yr), who during therapy maintained plasma GH and IGF-I concentrations under 5 µg/l and 450 µg/l, respectively, were considered as responders and studied for 24 (1 patient) to 36 months (6 patients). Three patients (1 male, 2 females, 46-61 yr) with levels of GH and IGF-I above those values were studied for 12 months. The OGTT (75 g po) and TRH test (400 µg iv) were repeated before and after 6, 12, 24 and 36 months. The GH response to OGTT was abnormal (nadir: >2 µg/l) at 6 and 12 months in poorly responsive patients. This response was normalized in all responsive patients. Nonetheless, 2 responsive patients showed abnormal GH values after OGTT once each throughout the 36-month study period. The GH response to TRH was characterized by great variability and exhibited unpredictable behavior throughout the study period both in responsive and in poorly responsive patients. Only 2 patients in the responsive group showed persistent normal GH levels (peak: ≤5 µg/l) after TRH for 3 yr. In conclusion, SR lanreotide treatment gave rise to a correct control of GH hypersecretion and to a normalization of GH response to oral glucose in 7 out of 10 patients, although it did not abolish the paradoxical reaction of GH to TRH in all responders. The effect of SR lanreotide on GH response to glucose tolerance test was not paralleled by GH response to TRH.

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INTRODUCTION

Acromegaly is associated with significant morbidity and mortality (1). The therapeutic aim of treating acromegaly is to eliminate hypersecretion of GH and IGF-I. Transsphenoidal pituitary surgery remains the preferred therapy (2), although it fails to cure 50% or more of the patients (3). Radiation therapy requires years to be effective and may cause trophic hormone insufficiency (4). Long-acting analogues of somatostatin, such as octreotide (5-7) and lanreotide (8-12), have been effectively used to treat acromegaly in patients previously treated with either surgery or radiation.

Key-words: Lanreotide, TRH test, oral glucose tolerance test, acromegaly.

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Normalization of GH levels is one of the best determinants of therapeutic outcome in acromegaly (13). This normalization implies the return of GH secretion to a normal 24-h secretion rate and the restoration of normal response to various stimuli. Information on lanreotide effects on GH response to stimuli in acromegaly is scanty so far. The abnormal GH response to an oral glucose overload has been found to be reduced in acromegalic patients chronically treated by slow-release (SR) lanreotide, although without reaching a complete suppression (14). Some authors have reported a reduction during SR lanreotide therapy in the paradoxical response of GH to TRH generally observed in acromegaly (8), although a complete abolition of this response was not found (14). Therefore, we performed this study to assess the GH response to oral glucose tolerance test (OGTT) and TRH stimulation test in a group of acromegalic patients before and after long-term SR lanreotide treatment.

MATERIALS AND METHODS

Patients

We studied the evolution of GH response to oral glucose load and iv TRH stimulation over 12-36 months of SR lanreotide therapy in 10 acromegalic patients who gave informed consent. Individual characteristics are summarized in Table 1. All patients presented pure GH-secreting tumors and had been treated by transsphenoidal incomplete surgical resection of the pituitary adenoma. The assessment of the activity of acromegaly was based on clinical examination, mean GH concentrations >5 µg/l and fasting serum IGF-I >450 µg/l.

Study design and drug administration

Patients received an im injection of 30 mg SR lanreotide (Somatulina, Laboratorios Lasa, Grupo Beaufour Ipsen, Barcelona, Spain) every 14 days. Dosage was increased to one 30 mg injection every 10 days in patients with IGF-I levels >450 µg/l or GH >5 µg/l (3 patients at 3 months, 1 patient at 6 months and 1 patient at 18 months). Baseline serum concentrations of GH and IGF-I, as well as free thyroxine, TSH, prolactin, HbA_{1c} and routine laboratory analysis (blood cell count, and renal-liver function) were assessed before and after 3, 6, 12, 24, 30 and 36 months of therapy. TRH and OGTT stimulation tests were performed before and after 6, 12, 24 and 36 months of SR lanreotide therapy.

TRH test and OGTT

Endocrine tests were begun at 09:00 h, after an overnight fast, with the subjects recumbent. An indwelling catheter was placed in a forearm vein and kept patent with a slow infusion of 0.9% NaCl. The OGTT was performed by giving an oral glucose load (75 g). Blood samples for glucose and GH were collected at 0, 30, 60, 90, 120 and 150 min. Each subject received TRH (TRH Prem, Zyma-Frumtost, Switzerland), 400 µg iv in bolus at time 0. Blood samples for GH, TSH and prolactin were collected at 0, 30, 60 and 90 min. OGTT and TRH test were performed in random order for every patient. During therapy, GH and IGF-I levels and endocrine tests were evaluated just before the next im injection of the somatostatin analogue.

A paradoxical response of GH in the TRH test was considered to be present when the GH peak after TRH administration was >5 µg/l (15). The abnormal GH response to OGTT was defined as GH concentrations >2 µg/l 60-150 min after oral glucose load.

Responsiveness to SR lanreotide

We considered that the control of the GH hypersecretion was obtained when the IGF-I concentration was <450 µg/l and the GH levels were <5 µg/l. These requirements were attained by 7 patients (2 of them with SR lanreotide 30 mg every 10 days), who were considered responders to SR lanreotide therapy. These patients were studied for 24 (1 patient) to 36 months (6 patients). However, there

Table 1 - *Main clinical and analytical features of acromegalic patients before starting SR lanreotide therapy.*

Patient no.	Age (yr), sex	BMI	Time from diagnosis (yr)	Diabetes mellitus	Hypertension	Previous therapy	Tumour status	Baseline GH (µg/l)	GH after OGTT (µg/l)	IGF-I (µg/l)	Paradoxical response to TRH	Interval between doses (days)	Responsiveness to SR lanreotide
1	59, F	33.0	3	Yes	No	TSA	Micro	5	4	711	Yes	14	Yes
2	58, F	23.7	6	No	Yes	TSA, Rt, Br, Oct	Macro	6.8	4	828	Yes	10	Yes
3	65, F	34.5	9	No	No	TSA, Br	Macro	4	5	495	No	14	Yes
4	51, F	32.4	4	No	No	TSA	Micro	3	2.5	923	Yes	14	Yes
5	71, F	22.9	12	No	Yes	TSA, Br, Oct	Micro	6	5	465	Yes	10	Yes
6	29, M	23.9	2	No	No	TSA, Oct	Micro	8.8	7	1507	Yes	14	Yes
7	45, M	27.5	9	No	No	TSA, Oct	Macro	5.7	3.5	788	No	14	Yes
8	50, M	26.3	10	Yes	Yes	TSA, Br	Macro	12	8	810	No	10	No
9	61, F	27.3	20	Yes	Yes	TSA, Rt, Oct	Micro	10	15	855	Yes	10	No
10	46, F	35.7	4	Yes	Yes	TSA	Macro	7.9	4	1024	Yes	10	No

BMI: body mass index (kg/m^2); GH: growth hormone; IGF-I: insulin-like growth factor type I; TSA: transsphenoidal adenomectomy (performed at least 5 months before this study); Rt: radiotherapy (at least 3 years before the study); Br: bromocriptine (at least 7 years before the study); Oct: octreotide (at least 1 year before the study).

were 3 patients (8, 9 and 10) with GH and IGF-I concentrations persistently above the mentioned values who were considered as non-responders and were studied for 12 months.

Hormone assays

Blood samples were centrifuged immediately and the plasma stored at -20 C. Human plasma GH concentration was determined by using an automated immunoenzymatic assay (AIA 1200, Tosoh, Tokyo, Japan). Maximal intra-assay and inter-assay coefficients of variation were 5.4% and 3.3%, respectively. The sensitivity of the GH assay was 0.1 μg/l. Plasma TSH and prolactin concentrations were also determined using the Tosoh immunoenzymatic assay. For TSH assay, the sensitivity was 0.06 μU/ml and the maximal intra-assay and inter-assay coefficients of variation were 3.3% and 3.4%, respectively. For prolactin assay, the sensitivity and maximal intra-assay and inter-assay coefficients of variation were 1 μg/l, 6% and 4.5%, respectively. The plasma IGF-I assay was performed after an ethanol-acid extraction by means of a commercially available radioimmunoassay kit (Nichols Institute, San Juan Capistrano, CA, USA). Maximal intra-assay and inter-assay coefficients of variation were 3.0% and 8.4%, respectively, and the sensitivity of the assay was 13.5 μg/l. Free thyroxine was measured by commercially available immunoenzymatic assay kits (AIA-PACK FT4, Tosoh, Tokyo, Japan) that use the automated system AIA-1200. Blood glucose concentration was measured by a hexokinase method (Boehringer Mannheim, Germany), and HbA_{1c} levels were measured by high performance liquid chromatography (Variant Bio-Rad Laboratories, Hercules, CA, USA).

Statistical analysis

Results are expressed as mean±SE. The area under curve (AUC) for GH and glucose after oral glucose load was calculated between 0 and 150 min by a trapezoidal method. For statistical evaluation of the basal hormonal levels and hormonal responses to stimuli before and after therapy, the obtained values were analyzed by using repeated measurement analysis of variance. Individual comparisons were performed by the Scheffe test and Fisher's least-significance difference test. The differences were considered to be significant at $p<0.05$.

RESULTS

Baseline hormonal concentrations

Pre-treatment GH concentrations in the seven responder patients were 5.6±0.7 μg/l. These concentrations were significantly reduced after 3 months of SR lanreotide therapy (1.7±0.6 μg/l, $p<0.001$) and this reduction remained stable throughout the 36 months of the study (1.6±0.5 μg/l at 6 months, 2.2±0.9 μg/l at 12 months, 1.9±0.5 μg/l at 24 months, 2.1±0.5 μg/l at 30 months, and 1.8±0.4 μg/l at 36 months, $p<0.001$ for all times). IGF-I concentrations in these patients were 816±132 μg/l before therapy and 313±47 μg/l ($p<0.001$) after 3 months of SR lanreotide administration. Values of IGF-I were maintained under 450 μg/l throughout the study (275±36 μg/l at 6 months, 317±56 μg/l at 12 months, 280±36 μg/l at 24 months, 263± 43 μg/l at 30 months, and 239±44 μg/l at 36 months, $p<0.001$ for all times).

In the group of three poorly responsive patients GH concentrations were 9.9±1.2 μg/l at baseline and reached a nadir of 5.9±1.5 μg/l at 6 months. Pre-treatment IGF-I values were 896±65 μg/l and were reduced to 662±90 μg/l after 3 months of SR lanreotide administration. However, at no moment during the first year of the study period were GH concentrations under 5 μg/l and IGF-I levels under 450 μg/l. Therefore, these patients were dropped from the study after twelve months of therapy.

There were no significant changes in free thyroxine concentration, blood cell count and kidney and liver function tests during treatment compared to the basal values in the two groups of studied patients (data not shown).

Responses to OGTT

Abnormal GH response to glucose load (nadir: >2 μg/l) was shown by all patients before therapy. Poorly responsive patients exhibited this abnormal response when examined at 6 and 12 months. Nevertheless, in the group of seven responders there was one patient (no. 5) who exhibited abnormal GH response to OGTT at month 12 and a further one (no. 3) who showed this response at month 24. The remaining OGTT performed in this group of acromegalic patients showed normal GH suppression.

Concentration *vs* time curves in responders are shown in Figure 1. During lanreotide therapy, GH response to OGTT was significantly ($p<0.01$) reduced from 0 to 150 min at all moments when OGTT was performed. The GH secretion AUC was significantly ($p<0.001$) decreased throughout the study period (Fig. 1A). On the other hand, glucose concentrations after oral glucose administration exhibited no significant variations at the majority of the determinations performed during the 3-year study period. Baseline and 2nd hour glucose concentra-

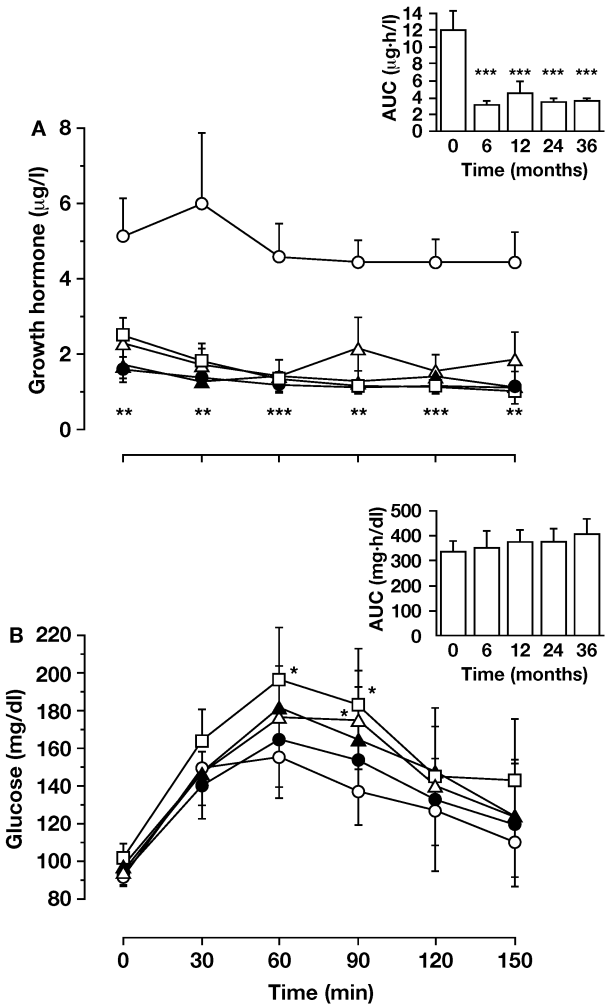

Fig. 1 - *Plasma GH (A) and glucose (B) responses to the oral glucose tolerance test (75 g) in the group of 7 responsive acromegalic patients before (open circles) and after 6 (closed circles), 12 (open triangles), 24 (closed triangles) and 36 months (open squares) of SR lanreotide therapy. Ordinate scale: GH (µg/l) and glucose (mg/dl) concentrations. Abscissa scale: time after glucose load (minutes). The insets show the AUC of GH (A) and glucose (B) secretion before and during SR lanreotide therapy. Each point or column represents the mean±SE. Values at 36 months are from 6 patients. *p<0.05, **p<0.01, ***p<0.001 vs values obtained before therapy.*

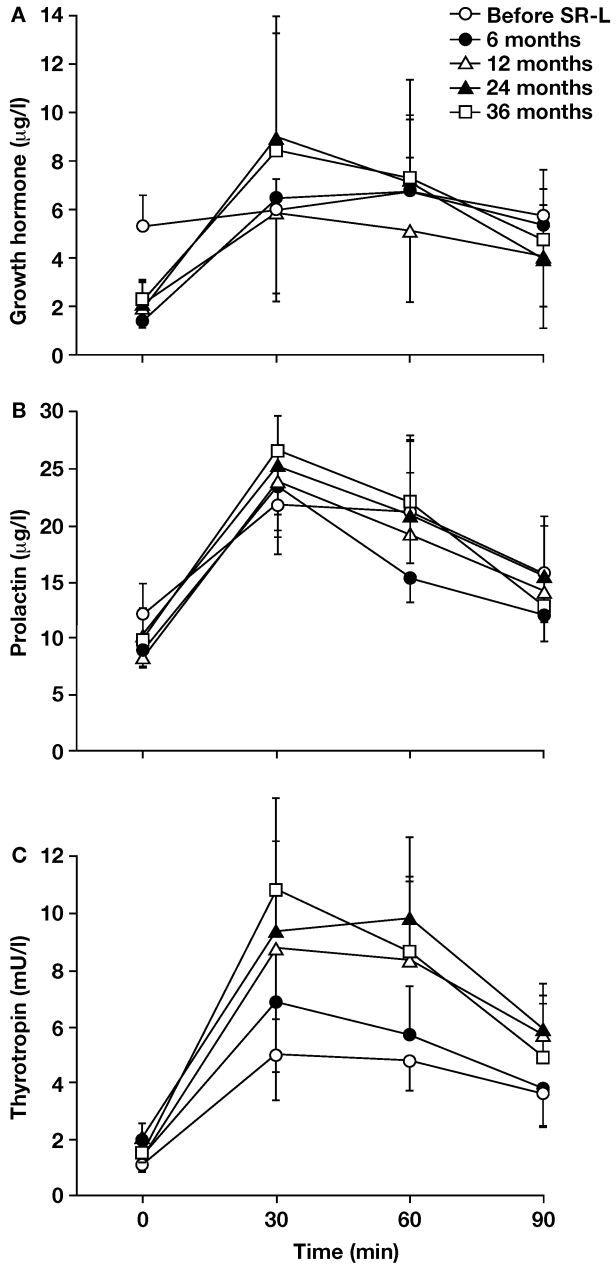

Fig. 2 - *GH (A), prolactin (B) and thyrotropin (C) responses to the intravenous administration of TRH (400 µg) in the group of 7 responsive acromegalic patients, before (open circles) and after 6 (closed circles), 12 (open triangles), 24 (closed triangles) and 36 months (open squares) of slow-release lanreotide (SR-L) therapy. Ordinate scale: plasma GH (µg/l), prolactin (µg/l) and thyrotropin (mU/l) concentrations. Abscissa scale: time (minutes). Each point represents the mean±SE. Values at 36 months are from 6 patients.*

tion and the glucose AUC did not show any significant changes throughout the 36 months of the study. We only found glucose values significantly higher ($p<0.05$) than those obtained before therapy at 60 min after 36 months, and at 90 min after 12 and 36 months (Fig. 1B). HbA_{1c} concentrations before therapy were 6.1±0.2%. These values did not show any significant change throughout the study period (5.9±0.2%, 5.9±0.2%, 6.0±0.1%, 6.3±0.2% and 6.2±0.2% at 3, 6, 12, 24 and 36 months, respectively).

Responses to TRH test

Seven patients (5 responders and 2 non-responders) exhibited paradoxical reaction of GH to TRH before starting SR lanreotide therapy. In the whole group, GH response during therapy was characterized by a great inter-individual variability. Only two patients (no. 1 and 2) in the responsive group showed persistent normal GH response after TRH for the 3 years of the study. One poorly responsive patient (no. 10) also exhibited normal response after 6 and 12 months of therapy. Patients no. 4 (responder) and no. 9 (non-responder) showed persistent paradoxical reaction to TRH at all times of the study. The remaining patients showed unpredictable behavior with regard to their GH response to TRH.

Concentration *vs* time curves in the seven responsive patients are depicted in Figure 2. When analyzing these patients as a group, no significant change in GH concentrations was found, except for baseline levels (Fig. 2A). Furthermore, baseline prolactin and TSH and their response to TRH stimulation did not show any significant variation throughout the study period in these patients (Fig. 2B and C).

DISCUSSION

Several investigators have shown the efficacy of SR lanreotide in the treatment of acromegaly. Plasma GH levels have been reported to be normalized in 43-89% of the patients (8, 9, 11, 14, 16-18), and IGF-I was suppressed to the normal range in 23-68% of the patients (8-12, 14, 16-19). In this study, 7 out of 10 acromegalic patients reached a good control of the disease during long-term SR lanreotide therapy. We found that IGF-I levels were suppressed to within the normal range in a higher percentage of patients than that reported by others (14, 16, 18) in patients treated for a shorter time. That percentage seems to be similar to those reported in patients treated for 1-3 years both with lanreotide (12) and octreotide (7). The effectiveness of treatment with somatostatin analogues appears to be modulated by the mode of treatment (5, 20) and the number of somatostatin receptors on somatotroph cells (21). Besides, the high percentage of normalization of GH and IGF-I in our study may also be explained by the moderate GH hypersecretion in most of our patients.

Our results show that GH suppression after OGTT was reached by all responders and that this suppression is maintained for a long time, with very few and sporadic exceptions. This suppression of GH is not accompanied by a clinically significant impairment of glucose tolerance. In the study by Johnson *et al.* (14), the increase of GH after oral glucose load was reduced in 8 patients treated for 6 months, but GH was suppressed to values under 2 µg/l in only 4 patients. In the report of Al-Maskari *et al.* (17) GH levels after OGTT were reduced after 6 months of SR lanreotide therapy to values of 4-5 µg/l in 10 acromegalic patients. Differences between our results and those reported by others may be accounted for by the selected population of responsive patients in this study.

Lanreotide infusion induced a transient inhibition of insulin and an increase in blood glucose in normal men (22). In acromegalics, carbohydrate tolerance has been reported to be unchanged (9, 17) or slightly worsened (8, 18) during lanreotide therapy. A progressively increasing trend in pre- and postprandial blood glucose and a slight decrease in serum insulin levels were found by Giusti *et al.* (10) in acromegalic patients treated during 6 months. The results in our responsive patients showed that there was no significant increment in the glucose AUC in the OGTT after SR lanreotide. HbA_{1c} concentrations remained unchanged throughout the 3 years of the study, as reported by Caron *et al.* (12). Therefore, long-term SR lanreotide therapy is not accompanied by a clinically significant worsening in carbohydrate tolerance.

TRH is considered to have no effect on GH levels in healthy humans (23). However, a high proportion of patients with acromegaly have a paradoxical GH release after TRH (24). This anomalous response has also been documented in certain pathological situations (15), so it seems that TRH is a non-specific GH stimulator and the GH release after TRH is considered to be a secondary criterion for the diagnosis of acromegaly. The mechanism of this response remains unknown. A direct pituitary stimulatory action (25) and an indirect effect, mediated via a decrease in the hypothalamic release of somatostatin or an increase in GHRH secretion (26), have been proposed as possibilities. Our results show that GH response to TRH has no relationship with the degree of control of the disease. In fact, we could not find any homogeneous pattern of response to TRH in our patients. On the contrary, GH reaction to TRH was unpredictable and characterized by a great inter- and intra-individual variability. Johnson *et al.* (14) investigated the GH response to TRH 7, 14 and 21 days after a 30 mg single injection of SR lanreotide. They observed that this response was reduced in 4 out of 8 patients, but in all cases it persisted. The magnitude of the GH reaction after TRH stimulation was also diminished in another group of 8 acromegalic patients treated by SR lanreotide for 6 months, but in none was the response

to TRH normalized. Similarly, GH response to TRH was reduced by more than 50%, but remained present in the group of patients studied by Marek *et al.* (16). Our results and those of others suggest that certain abnormalities of GH secretion may persist in acromegalic patients, despite normalization of IGF-I levels (27, 28). As reported in previous studies, we found no modifications in baseline levels of prolactin (8, 10) and TSH (9, 10, 12, 16) and their increase after TRH administration (8).

Although there is no universally accepted definition of normalization of GH secretion in acromegalic patients, several ways to evaluate GH-IGF-I axis during therapy with somatostatin analogues have been employed. We attempted to assess the potential clinical usefulness of OGTT and TRH test as predictive parameters for sensitivity to somatostatin analogues. Data in responsive patients treated for 2-3 years enable us to deduce some conclusions. Firstly, GH response to OGTT was found to be uniform, consistent and with few changes throughout a long period of time. This implies that the OGTT seems to be reliable and reproducible, *i.e.* somatostatin analogues responsive patients show a uniform pattern of GH response to oral glucose load and this test may be used in monitoring patients during therapy. Secondly, GH response to TRH was unpredictable in both responsive and poorly responsive patients. We found no relationship between TRH-induced GH release and the control of the acromegalic disease. Therefore, the TRH test seems to be inadvisable in the evaluation of acromegalic patients under chronic SR lanreotide treatment. In summary, despite the limitation of this study derived from the restricted number of acromegalic patients, our present results show that GH response to OGTT was uniform throughout time in lanreotide responsive patients and OGTT might be a good predictor for sensitivity to therapy. However, performing repeated TRH tests in the evaluation of treated acromegalic patients seems to be useless.

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