CLINICAL STUDY

Limited predictive value of an acute test with subcutaneous octreotide for long-term IGF-I normalization with Sandostatin LAR in acromegaly

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Abstract

Objectives: To study whether the growth hormone (GH) response after the subcutaneous administration 50 µg of octreotide (acute octreotide test) has any predictive value for long-term IGF-I normalization with Sandostatin LAR.

Design: Twenty four therapy-naïve patients with active acromegaly were studied.

Results: > 75% GH decrease in the acute octreotide test predicted long-term IGF-I normalization with Sandostatin LAR in 8/11 (73%) of patients. 3/13 (23%) patients with < 75% GH decrease in the acute octreotide test were long-term biochemically controlled with Sandostatin LAR. Using the > 75% GH reduction criterion, the sensitivity and specificity of this test for predicting long-term normalization of serum IGF-I with Sandostatin LAR treatment were 73% and 77%, respectively (positive and negative predictive values: 73% and 77%, respectively). 6/8 (75%) patients with GH suppression to levels < 1.1 µg/l and 9/16 (56%) patients with GH suppression to levels < 2 µg/l in the acute octreotide test showed normalization of serum IGF-I with long-term Sandostatin LAR treatment. The sensitivity and specificity of GH suppression < 1.1 µg/l for predicting of the long-term normalization of serum IGF-I with Sandostatin LAR therapy were 55% and 85%, respectively (positive and negative predictive values: 75% and 69%, respectively). The sensitivity and specificity of GH suppression < 2 µg/l for predicting of the long-term normalization of serum IGF-I with Sandostatin LAR therapy were 82% and 46%, respectively (positive and negative predictive values: 56% and 75%, respectively).

Conclusion: The acute octreotide is not recommended for clinical decision making with regard to long-term treatment using the long-acting somatostatin analog Sandostatin LAR in acromegaly.

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Introduction

Acromegaly is a chronic and debilitating disorder, which is almost uniquely caused by growth hormone (GH) hypersecretion from a pituitary adenoma (1). Serum insulin-like growth factor I (IGF-I) has been used both as a screening tool and as a tool for clinical monitoring of therapeutic response in patients with acromegaly (2).

Historically, pituitary surgery has been used as first-line treatment for acromegaly. With this treatment, cure rates have been the greatest for microadenomas (ranging from 70 to 80%), but for macroadenoma surgery success rates less than 50% have been reported (3).

Nowadays, medical treatment for acromegaly consists of dopamine agonists, somatostatin analogs, GH

receptor antagonists or combinations. Long-acting somatostatin analogs are increasingly being appreciated as first-line therapies for active acromegaly especially for those patients in whom an operation will not likely result in complete cure or in those patients with contraindications for operation (4–7). In the past, acute tests have been designed for predicting the long-term response of the tumoral GH secretion to short-acting somatostatin analogs. Whether acute tests adequately predict these long-term responses is debatable (8–10). The potential predictive value of acute tests for the long-term response to long-acting depot formulations of somatostatin analogs has only been studied very recently by Karavitaki and co-workers (11). In their studies, an acute octreotide test was reliable in predicting 'safe' GH levels in patients treated with long-acting octreotide (Sandostatin LAR),

although it was less reliable for predicting this on long-acting lanreotide (Somatulin Autogel, or Somatuline LA).

In the present study we have determined whether an acute test using a single subcutaneous dose of octreotide is useful for predicting long-term normalization of serum IGF-I levels with Sandostatin LAR.

Patients and methods

Patients

Twenty four patients (13 females, 11 males, 24–79 years old at diagnosis, mean age at diagnosis 56 years) with active acromegaly were enrolled in these studies. The diagnosis of active acromegaly was made on the basis of typical clinical features and/or non-suppressed GH after an oral glucose load and IGF-I levels above the age- and sex-adjusted reference range of the assay and the presence of a pituitary tumor at neuroradiology. The patients had not previously been treated with somatostatin analogs, nor with dopamine agonists or GH receptor antagonists and were not operated upon nor had received pituitary radiotherapy. They were treated with Sandostatin LAR (Novartis Pharma, Basle, Switzerland) administered intramuscularly in dosages ranging from 10–30 mg every 4 weeks. The dosage was titrated until the maximum dosage of 30 mg Sandostatin LAR per month was reached, or until normalization of serum IGF-I levels was achieved. Patients were maintained on Sandostatin LAR treatment for at least 9 months. All patients gave their informed consent to participate in these studies.

Test protocol and follow-up

Fifty micrograms of octreotide was administered subcutaneously and blood samples were drawn for GH measurements at 15 min before and 15, 45, 105, 165, 225, 285, 345, 405 and 465 min after administration of the drug. On a control day, samples for GH measurements were drawn at the same time intervals, but no drug was administered. The response to octreotide was calculated using the mean of the 45–465 min GH measurements or mean 45–225 min measurements. GH measurements were expressed as percentage of the GH measurements over the same time interval on the control day. As defined previously, a positive GH response in this test had been arbitrarily defined as >75% decrease of the mean 45–465 min or 45–225 min GH levels (12). We also have looked at a less stringent GH decrease amounting to more than 50%. The GH nadir response was also evaluated.

For long-term follow-up, serum IGF-I was used as parameter for biochemical control. Gender- and age-dependent cut-off levels, as supplied by the manufacturers of the assay, were used.

Assays

Serum GH levels were measured by a two-site chemiluminescent immunometric assay (Immulite; Diagnostic Products Corp., Los Angeles, CA, USA) (intra-assay CV 6.0%, inter-assay CV 5.7%). Serum IGF-I levels were measured by a non-extraction immunometric assay supplied by Diagnostic Systems Laboratories Inc. (Webster, TX, USA) (intra-assay CV 3.9%, inter-assay CV 4.2%).

Results

Patients and GH and IGF-I levels

In the 24 patients, basal serum GH levels were $19.0 \pm 26.6 \mu\text{g/l}$ (mean $\pm$ s.d.), serum GH levels were $18.3 \pm 20.2 \mu\text{g/l}$ (mean $\pm$ s.d.) in the 45–465 min sampling interval and $18.0 \pm 20.2 \mu\text{g/l}$ (mean $\pm$ s.d.) in the 45–225 min sampling interval, both on a control day. Mean basal serum IGF-I levels were 153.6 nmol/l. Overall, in 11 out of these 24 patients (46%), serum IGF-I levels normalized with Sandostatin LAR therapy at long-term (>9 months) follow-up.

Acute octreotide test and long-term follow-up

Sampling intervals and GH decrease after octreotide Eleven of the 24 patients (46%) showed >75% GH decrease in the acute octreotide test within the 45–465 min, or 45–225 min GH sampling intervals. At follow-up, eight out of these 11 patients (73%) showed an adequate suppression of serum IGF-I to levels within the reference range with long-term Sandostatin LAR treatment.

Thirteen out of the 24 patients (54%) did not show >75% GH response in the acute octreotide test. Three out of these 13 patients (23%) showed normalization of serum IGF-I with long-term Sandostatin LAR treatment.

Using the >75% GH reduction criterion, the acute octreotide test had a sensitivity of 73% and a specificity of 77% for predicting long-term normalization of serum IGF-I with Sandostatin LAR treatment. Results were similar for both GH sampling intervals (45–465 min or 45–225 min GH sampling). Using this criterion, the positive predictive value of the acute octreotide test for the long-term normalization of serum IGF-I with Sandostatin LAR treatment was 73% and the negative predictive value was 77% (Table 1).

Nineteen out of the 24 patients (79%) showed >50% decrease in the acute octreotide test within the 45–465 min GH sampling interval and 20 patients (83%) within the 45–225 min GH sampling interval. At follow-up, 11 of these patients (58% of patients with the 45–465 min GH sampling interval, or 55% of patients with the 45–225 min GH sampling interval) showed an adequate suppression of serum

Table 1 The acute 50 µg octreotide test. Prognostic profiles (%) of various GH suppression values.

	45–465 min GH suppression >75%	45–225 min GH suppression >75%	45–465 min GH suppression >50%	45–225 min GH suppression >50%	GH nadir <1.1 µg/l	GH nadir <2 µg/l
Sensitivity	73	73	100	100	55	82
Specificity	77	77	38	31	85	46
Positive predictive value	73	73	58	55	75	56
Negative predictive value	77	77	100	100	69	75

IGF-I to levels within the reference range with Sandostatin LAR.

Five out of the 24 patients (21%) did not show >50% GH decrease in the acute octreotide test within the 45–465 min GH sampling interval and four patients (17%) within the 45–225 min GH sampling interval. None of these patients showed normalization of serum IGF-I with long-term Sandostatin LAR treatment.

Using the >50% GH reduction criterion, the acute octreotide test had a sensitivity of 100% and a specificity of 38% for predicting long-term normalization of serum IGF-I with Sandostatin LAR therapy for the 45–465 min GH sampling period. For the 45–225 min GH sampling period, these values were 100% and 31% respectively. Using this criterion, the positive predictive value of the acute octreotide test for the long-term normalization of serum IGF-I with Sandostatin LAR therapy was 58% for the 45–465 min GH sampling period and 55% for the 45–225 min GH sampling period and the negative predictive value was 100% for both sampling periods (Table 1).

GH nadir after octreotide The nadir GH levels in the acute octreotide test were 5.1 ± 11.9 µg/l (mean $\pm$ S.D.), range 0.2–58.9 µg/l with a percentage decrease of 74% as compared with baseline GH levels. The time to achieve nadir was 142 ± 99 min (mean $\pm$ S.D.).

In the acute octreotide test, GH suppression to levels <1.1 µg/l was achieved in eight out of 24 patients (33%). six out of these eight patients (75%) showed normalization of serum IGF-I with long-term Sandostatin LAR treatment, whereas two (25%) did not. This level of GH suppression (GH <1.1 µg/l) had a sensitivity of 55% and a specificity of 85% for predicting of the long-term normalization of serum IGF-I with Sandostatin LAR therapy. The positive and negative predictive values were 75% and 69% respectively (Table 1).

Less stringent GH suppression to levels <2 µg/l in the acute octreotide test was achieved in 16 out of 24 patients (66%). Nine out of these 16 patients (56%) showed normalization of serum IGF-I with long-term Sandostatin LAR treatment, whereas seven (44%) did not. This level of GH suppression (GH <2 µg/l) had a sen-

sitivity of 82% and a specificity of 46% for predicting of the long-term normalization of serum IGF-I with Sandostatin LAR therapy. The positive and negative predictive values were 56% and 75% respectively (Table 1).

Discussion

Historically, pituitary (sub)total adenomectomy used to be the primary treatment for active acromegaly. In the late sixties and early seventies of the past century, dopamine agonists were introduced for the medical treatment of prolactinomas and GH-secreting adenomas (1, 13). In the early eighties of the same century, octreotide was introduced as medical treatment for acromegaly, either as primary treatment or as adjunctive treatment after unsuccessful surgery. Because of their superiority to dopamine agonists, somatostatin analogs are currently considered as the first-line medical treatment of acromegaly (1, 14, 15). Recently, the GH receptor blocking drug pegvisomant has been introduced for the treatment of those patients with acromegaly who are not responsive to somatostatin analogs or are intolerant to these drugs (16, 17).

Many studies have evaluated the effects of somatostatin analogs in active acromegaly (5, 18–32). The different criteria, which have been used to define the response to medical treatment, make it almost impossible to compare these studies. Also, newer, more sensitive GH and IGF-I assay techniques have been introduced over time. Suppression of GH to levels below 2.5, 2.0 and 1.0 µg/l have been used as criteria for sufficient response to medical treatment (22, 33). In our study, only normalization of serum IGF-I was used as the sole indicator of chronic control with medical treatment.

In previous studies, the long-term efficacy of short-acting and long-acting somatostatin analogs in sufficiently suppressing GH levels and/or normalizing IGF-I levels varied from 38 to 79% (5, 19, 21, 24–32). However, in some of these studies, patients treated with long-acting somatostatin analogs had been selected on the basis of a positive response to short-acting analogs (5, 21, 28). In our series of unselected therapy-naïve patients, 46% of patients were controlled with Sandosta-

tin LAR at long-term follow-up, as monitored by normalization of serum IGF-I.

In the present study, more than 75% GH suppression in the acute octreotide test had a sensitivity of 73% and a specificity of 77% for predicting normalization of serum IGF-I with Sandostatin LAR therapy (positive predictive value 73%, negative predictive value 77%). As could be expected, using less stringent GH suppression (> 50%) in this test resulted in an increased sensitivity but decreased specificity (sensitivity 100%, specificity 31–38%, positive predictive value 55–58%, negative predictive value 100%).

Twenty three percent of patients who demonstrated < 75% GH response, but none of the patients who demonstrated < 50% GH response to the acute administration to octreotide long term showed normalization of serum IGF-I with long-term Sandostatin LAR therapy.

In a study by Colao and co-workers, the sensitivity and specificity of an acute octreotide test for the long-term control by subcutaneously administered octreotide were 71% and 55%, respectively (9). In this study, response was defined as GH-suppression to serum levels < 5 µg/l at follow-up. The positive and negative predictive values for the acute octreotide test in their study were 53% and 78% respectively (9). In a recent study by Karavitaki and co-workers, the positive predictive value for an acute octreotide test for normalization of serum IGF-I was 60% for Somatuline Autogel, or Somatuline LA and 77% for Sandostatin LAR when suppression of GH levels in the acute test to < 6.05 mU/l and < 5.25 mU/l respectively, was used as criterion (11).

The mean nadir GH level in the acute octreotide test in these studies were 2.5 mU/l (percentage decrease 85%), which compares well with our mean value amounting to 5.1 µg/l (percentage decrease 74%). The mean time to achieve GH nadir in the study by Karavitaki and co-workers was 228 min (11) and in our studies it was 142 min.

In conclusion, the acute octreotide test generally predicts the long-term biochemical response to Sandostatin LAR. However, also 23% of the patients who demonstrated less than 75% decrease in GH levels to the acute administration to octreotide, or 31% of the patients who did not demonstrate GH suppression to levels < 1.1 µg/l, or 25% of the patients who did not demonstrate GH suppression to levels < 2 µg/l (25%) were still chronically controlled with Sandostatin LAR. Like other authors (9), we do not recommend acute octreotide tests. Whether this recommendation also holds for acute tests with newer (receptor specific, or universal) somatostatin analogs cannot be derived from the present study.

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