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-naive 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 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 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.

European Journal of Endocrinology 153 67–71

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 octreo-
tide 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-sup-
pressed 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 neu-
oradiology. The patients had not previously been trea-
ted with somatostatin analogs, nor with dopamine
agonists or GH receptor antagonists and were not oper-
ated upon nor had received pituitary radiotherapy.
They were treated with Sandostatin LAR (Novartis
Pharma, Basle, Switzerland) administered intramuscu-
larly 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 treat-
ment 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 subcu-
taneously 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 adminis-
tration 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 octreo-
tide was calculated using the mean of the 45–465 min
GH measurements or mean 45–225 min measure-
ments. GH measurements and 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 manu-
facturers of the assay, were used.

**Assays**

Serum GH levels were measured by a two-site chemi-
luminescent immunometric assay (Immulite; Diagnos-
tic 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±26.6 μg/l (mean±S.D.), serum GH levels were
18.3±20.2 μg/l (mean±S.D.) in the 45–465 min
sampling interval and 18.0±20.2 μg/l (mean±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 normali-
zation 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
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±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±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 the long-term normalization of serum IGF-I with Sandostatin LAR therapy. The positive and negative predictive values were 75% and 82% 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 sensitivity 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 untreated therapy-naive 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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Received 28 February 2005
Accepted 22 March 2005