Abnormal growth hormone secretion: clinical aspects
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Chapter 2

Octreotide Long-Acting Repeatable and Lanreotide Autogel are equally effective in controlling growth hormone secretion in acromegalic patients

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Abstract

Objective Recently a new depot preparation of the long-acting somatostatin analogue, lanreotide Autogel was introduced for the treatment of acromegaly. Like octreotide long-acting repeatable (LAR), it has high binding affinity for the somatostatin receptor subtype SSTR 2 and less binding affinity for SSTR 5. We hypothesized that the ability to suppress GH secretion in patients with acromegaly would be similar for these depot preparations.

Patients and study design Seven patients (mean age 48.4 ± 7 yr) on long-term octreotide LAR treatment at a monthly injection interval for a mean of 2.8 yr were enrolled in the study. They underwent a GH secretory profile study with 10 min sampling for 24 hr, 28 days after an injection. At two, four and six weeks after the next injection fasting GH profiles (every 30 min for 3.5 hours) and serum IGF-I measurements were measured. These investigations were repeated 12 months later, when the patients were on an individually titrated stable dose of lanreotide Autogel.

Results Secretory characteristics and total 24 h GH secretion, estimated by deconvolution analysis of the 10 min 24 h plasma GH concentrations, did not show differences between these two long-acting somatostatin analogues. Both drugs were equally effective in GH and IGF-I suppression as measured at 2, 4 and also at 6 weeks following an injection.

Conclusion The efficacy of lanreotide Autogel and octreotide LAR was equal, notwithstanding that these drugs are administered in a different way and have different pharmacokinetics.
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Introduction

Acromegaly is a syndrome caused by overproduction of growth hormone (GH) from a GH-secreting pituitary adenoma. The high levels of GH and IGF-I are associated with increased morbidity and mortality, which necessitates adequate control of the disease (1,2). Although transsphenoidal microsurgery is the first choice treatment in eligible patients, somatostatin analogues are the preferred secondary therapy in the 30-40% of patients not in remission after surgery and in the 10-15% who develop recurrence of disease during long-term follow-up(1,3,4). Furthermore, primary treatment of acromegaly with somatostatin analogues is increasingly applied (5).

Somatotrope adenomas express high levels of somatostatin receptor subtypes SSTR 2 and 5 (6,7). The somatostatin analogues octreotide (Novartis Pharma AG, Basel Switzerland) and lanreotide (Ipsen Biotech, Paris, France) both have high binding affinity for the SSTR 2 and to a lesser extent for the SSTR 5 (8). Octreotide LAR, the depot preparation of octreotide given by monthly i.m. injections is able to normalize GH concentrations in 56% and IGF-1 in 66% of the patients (9). Lanreotide Slow Release (SR), the more frequently i.m. injected depot preparation of lanreotide, seems less effective in normalizing GH and IGF-I concentration (10-13). Recently, lanreotide Autogel, a new slow-release depot preparation of lanreotide was introduced. This new delivery formulation is available in small-volume, prefilled syringes, and is administrated by monthly deep s.c. injections (14).

Considering the comparable binding affinity of octreotide and lanreotide for SSTR’s, we hypothesized that there would be no difference between the two depot preparations in their ability to suppress GH secretion in patients with acromegaly. To test this hypothesis, we applied two different independent approaches: first by measuring GH secretion characteristics via deconvolution analysis of 24 h plasma GH concentrations profiles. We have recently shown that sustained blockade by octreotide can not restore all these parameters of abnormal GH secretion, but we have not established that for lanreotide (15). Secondly, we evaluated the extent and duration to which both depot somatostatin
analogues suppressed GH and IGF-I secretion.

Methods

Patients
For this study we included 7 patients with active acromegaly (of whom two were studied previously), who showed relatively good responsiveness to octreotide(15). The diagnosis was based on the characteristic clinical features and confirmed by insufficient suppression of GH concentration during the glucose tolerance test, the presence of a pituitary adenoma on radiological imaging, and elevated age-adjusted IGF-I concentrations. The clinical characteristics of the patients are described in Table 1. All patients used octreotide LAR (20 or 30 mg, at a monthly scheme) for an average duration of 2.8 years. None of the patients received a dopamine agonist before or during the study. Although the treatment goals were similar for both analogues, i.e. GH < 5 mU/L and a normal age-related IGF-I, four out of seven patients were using 20 mg of octreotide LAR, whereas six patients required the highest dose (120 mg) of lanreotide. The patients were first titrated on octreotide LAR. When there was a discrepancy between GH and IGF-I concentrations we gave preference to IGF-I, at least when the clinical response was satisfactory. The resultant octreotide LAR dose required was 20 mg in four, and 30 mg in three patients. Three out of four patients already had reached the treatment goals, and the fourth patient did not have better results on 30 mg octreotide LAR. The local Medical Ethical Committee approved the protocol and all patients gave written informed consent.

Study protocol (Figure 1)
The patients were investigated in a prospective study design according to the following protocol. The patients were first analysed on their regular octreotide LAR treatment. To assess details of GH secretory characteristics during chronic octreotide treatment, a 24 h plasma GH profile (with 10 min intervals) was performed 4 weeks after an octreotide LAR injection. To assess the extent and duration of GH suppression
Octreotide and lanreotide are equally effective in controlling GH secretion during chronic treatment fasting morning GH profiles were obtained at 2, 4 and 6 weeks after the last octreotide LAR injection. Subsequently, patients were included in a Phase II International Multicentre Trial for Evaluating the Efficacy and Safety of Lanreotide Autogel (Data on file Ipsen –Beaufort, study E2852030717). Patients were randomised to receive 60, 90, or 120 mg of lanreotide Autogel, the dose of which was subsequently adjusted according to individual fasting GH profiles and IGF-I concentrations during the course of the trial aiming at a serum GH concentration < 5mU/L and a normal IGF-1 for age. Six of the seven patients required the highest lanreotide dose. At the end of the international trial, one year later, the investigations were repeated, i.e. a 24 h plasma GH profile 4 weeks after a lanreotide Autogel injection followed by a GH profile 2, 4 and 6 weeks after an injection. Radiological imaging (MRI or CT scan) of the pituitary was performed before the start on each analogue and twice during follow up.

Figure 1. Study protocol.
**Study parameters**

*24 hours GH profile*

Patients were hospitalised the evening before the sampling studies, 27 days after the last injection with octreotide LAR or lanreotide Autogel. The following morning, an intravenous cannula was inserted into a large forearm vein, and blood samples were withdrawn at 10-min intervals for the next 24 h, starting at 9.00 h. Standard meals were served at predetermined time points, 7.30 h, 11.30 h and 17.30 h. Lights were turned off between 22.00 h and 07.00 h. All plasma samples were frozen immediately and stored at $-20^\circ$C until analysis.

*Short-withdrawal study*

After an overnight fast, patients were admitted to the Clinical Research Centre of the Department of Endocrinology between 08.00 and 09.00 h. An intravenous catheter was inserted in a forearm vein for collection of all blood samples. The patients were fasting during the blood sampling procedure. From the first blood sample plasma IGF-I concentration was determined. Subsequently, blood samples were obtained every thirty minutes for 3.5 hours. The mean GH was calculated from 8 samples. All samples from the patients were stored at $-20^\circ$C until analysis in the same GH and IGF-I assay runs.

*Assays*

GH concentrations were measured with a sensitive time-resolved fluoro-immunoassay (Wallac, Turku, Finland) specific for the 22-kDa GH. The standard was recombinant human GH (Genotropin, KabiVitrium, Uppsala, Sweden), which was calibrated against the WHO First International Reference Preparation 80/505. To convert mU/L to µg/L, divide by 2.6. The limit of detection (defined as the value 2 SD above the mean value of the zero standard) was 0.03 mU/L. The intra-assay coefficient of variation (CV) ranged from 1.6 to 8.4 % in the assay range between 0.26-47 mU/L, with corresponding inter-assay CV’s of 2.0 –9.9 %. The total serum IGF-I concentration was measured by IRMA after dissociation and blocking of the IGF-binding proteins with IGF-
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II. (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The reference values (95% CI) per decade ranged from 11-77 nmol/l for 20-30 yrs, 10-42 nmol/l for 30-40 yrs, 8-33 nmol/l for 40-50 yrs, 8-24 nmol/l for 50-60 yrs and 8-22 nmol/l for 60-70 yrs.

Analytical techniques
Multiparameter deconvolution analysis was used to quantify basal GH secretion and the GH half-life (16). This waveform-specific technique estimates the rate of basal release, the number and mass of randomly ordered secretory bursts, and the subject-specific (mono-exponential) half-life (17). The daily secretion rate is the product of secretory burst frequency and mean mass of GH released per event. Total GH secretion is the sum of basal and pulsatile secretion (16). (17)

Statistical Analysis
Data are given as the mean ± SEM, unless otherwise noted. Statistical analysis were carried out using Student’s t-test when applicable and with multivariate repeat measures analysis to compare differences between and within groups. Calculations were performed with SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL). P < 0.05 was considered significant.
Results

All patients completed the study. Chronic treatment with lanreotide Autogel was well tolerated by all patients, as was octreotide LAR treatment. Three patients experienced bowel cramps and diarrhoea for several days after the first injections of lanreotide Autogel, resolving after the fourth injection. No adverse events were reported during the study.

Of the three patients who had previous surgery, no change in residual tumor volume was noted on both analogues. In one out of four non-operated patients, a 50% decrease in tumor volume was found during octreotide LAR treatment, but no further change in tumor volume could be detected in these patients during subsequent lanreotide treatment.

24 hour plasma GH Profile

Fig.1 describes the 24 h plasma GH concentrations of all seven patients during treatment with both somatostatin analogues, showing a remarkable similar pattern. The secretory characteristics as analysed by deconvolution analysis were similar during both treatments and are detailed in Table 2. The pulsatile and total GH secretion per 24 h were not different between octreotide LAR and lanreotide Autogel.
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**Short withdrawal study**

Table 3 describes the mean GH levels and IGF-I concentrations during the 6 weeks of withdrawal. Mean GH and IGF-I levels obtained 2, 4, and 6 weeks were not different between the two treatment groups. In time, no significant changes in GH levels and IGF-I concentrations could be detected within the two treatments.

The number of patients achieving both control of GH and IGF-I were three under both treatment modalities. In only one patient of the remaining four, GH was normal on octreotide and slightly elevated on lanreotide, achieving concordance on both criteria in six out of seven patients.

Six weeks after a lanreotide Autogel and octreotide LAR injection only one had a normal mean GH and IGF-I for age.

**Table 2. Deconvolution of 24 h secretory GH profiles in acromegalic patients on treatment with octreotide LAR and lanreotide Autogel.**

<table>
<thead>
<tr>
<th></th>
<th>Octreotide LAR</th>
<th>Lanreotide Autogel</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretory half duration (min)</td>
<td>27.8 ± 2.9</td>
<td>28.1 ± 3.3</td>
<td>0.95</td>
</tr>
<tr>
<td>Half life (min)</td>
<td>16.5 ± 1.5</td>
<td>15.1 ± 1.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Number of secretory bursts/24 h</td>
<td>36 ± 1.2</td>
<td>37 ± 1.7</td>
<td>0.50</td>
</tr>
<tr>
<td>Interburst interval duration (min)</td>
<td>40.3 ± 1.2</td>
<td>38.7 ± 1.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Secretory-burst amplitude (mU/L/min)</td>
<td>0.27 ± 0.06</td>
<td>0.29 ± 0.06</td>
<td>0.51</td>
</tr>
<tr>
<td>Burst mass (mU/L)</td>
<td>8.59 ± 2.46</td>
<td>9.02 ± 2.43</td>
<td>0.80</td>
</tr>
<tr>
<td>Basal secretion (mU/L/24 h)</td>
<td>2.46 ± 0.91</td>
<td>2.69 ± 1.14</td>
<td>0.49</td>
</tr>
<tr>
<td>Pulsatile secretion (mU/L/24 h)</td>
<td>296 ± 78</td>
<td>337 ± 91</td>
<td>0.34</td>
</tr>
<tr>
<td>Total secretion (mU/L/24 h)</td>
<td>543 ± 166</td>
<td>606 ± 199</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM. Statistical comparisons were made with the paired Student's *t*-test.
Table 3. Mean GH and IGF-1 concentrations in acromegalic patients obtained 2, 4, and 6 weeks after injection of octreotide LAR or lanreotide Autogel.

<table>
<thead>
<tr>
<th>Weeks after injection</th>
<th>Octreotide LAR</th>
<th>Lanreotide Autogel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean GH (mU/L)</td>
<td>IGF-1 (nmol/L)</td>
</tr>
<tr>
<td>2</td>
<td>6.5 ± 1.8</td>
<td>46 ± 9</td>
</tr>
<tr>
<td>4</td>
<td>7.7 ± 2.0</td>
<td>40 ± 4</td>
</tr>
<tr>
<td>6</td>
<td>10.1 ± 2.3</td>
<td>47 ± 10</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SEM. Statistical calculations were performed with multivariate repeat measures analysis. For mean GH levels no differences were found between lanreotide and octreotide treatment (P=0.53) and GH concentrations did not change in time (P=0.33). The interaction term (time x drug) was non-significant (P=0.53). For IGF-1 comparable results are shown. The P-values were 0.39, 0.43 and 0.34, respectively.

Discussion

This study is the first report that compares lanreotide Autogel, a new slow release formulation, with octreotide LAR. Both drugs are long-acting octapeptide depot somatostatin analogues used for the treatment of acromegaly (14,18). Both analogues showed similarly suppressed GH levels during a detailed 24 h study. Moreover, during the regular injection interval (2 and 4 weeks) and also 6 weeks after the injection, both drugs equally suppressed mean serum GH and IGF-I concentrations. The results from this study on lanreotide Autogel differ from previous studies, comparing lanreotide SR with octreotide LAR. Octreotide LAR, using one monthly injections generally seems to show a higher efficacy in suppressing serum GH and IGF-I levels than lanreotide SR, injected i.m. every 7-21 days (10-13). Lanreotide SR, however, is a different
Octreotide and lanreotide are equally effective in controlling GH secretion preparation than lanreotide Autogel. Lanreotide SR consists of lanreotide incorporated into micro particles (like octreotide LAR) and is injected intramuscularly. In contrast, lanreotide Autogel consists of lanreotide-acetate dissolved in water, and is injected deep-subcutaneously. Pharmacokinetic studies of lanreotide Autogel in healthy subjects have shown a release pattern with an almost log-linear decrease of lanreotide serum levels after a single subcutaneous injection, with a terminal half-life of approximately 4 weeks (unpublished data from Ipsen-Beaufour). There is no evidence of accumulation of lanreotide after multiple doses at any dose neither in healthy subjects nor in patients. Steady state serum lanreotide levels are reached after 4 doses in most patients (unpublished data from Ipsen-Beaufour). To date, therapeutic lanreotide levels (>1000 ng/L) in patients under chronic treatment were documented only 30 days after an injection. On the contrary, octreotide levels following a single octreotide LAR injection show a totally different release pattern: immediately after injection there is a small peak followed by an increase in octreotide levels after 7 days reaching a maximum at 28 days, while therapeutic octreotide levels (>600 ng/L) are maintained up to 42 days (19). These differences in pharmacokinetics between the two depot somatostatin analogues apparently do not result in different efficacy to suppress GH secretion.

In order to obtain the best possible assessment of the GH suppressive effect of both analogues we used detailed 24 hr data analyzed with deconvolution analysis. Both depot preparations are registered for clinical use with an injection interval of 4 weeks, implicating that a safe suppression of GH and IGF-I is guaranteed up to 28 days after an injection in octreotide or lanreotide sensitive patients. Hence, we considered this time point to be the optimal time point for evaluation of GH secretory profiles in patients on chronic octreotide LAR or lanreotide Autogel treatment. The 24 h GH deconvolution analyses illustrate that both long-acting somatostatin analogues, octreotide LAR and lanreotide Autogel induced comparable suppression of GH secretion. Our in vivo data are thus in accordance with the in vitro data showing equal binding affinity for the SSTR 2 and 5 (8).

Recently we showed that patients who had well-controlled GH and IGF-
Figure 2. Individual 24 h GH concentration of each patient measured 28 days after the last injection with lanreotide Autogel (straight line) or octreotide LAR (dotted line).
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I levels with monthly octreotide LAR injections, remained well-controlled in the long-term when the injection interval was extended to six weeks (20). Octreotide LAR and lanreotide Autogel showed similar GH and IGF-I suppression at 2, 4 and 6 weeks. Although the measurements after four weeks showed a small increase in mean GH and IGF-1 concentrations in lanreotide treated patients, this was not statistically significant. Furthermore, mean simulated GH profiles calculated from 8 comparable time points during the 24h sampling studies and the IGF-I concentrations were statistically similar to the data obtained at 4 weeks of the withdrawal experiment. Therefore, it might be worthwhile to explore the extension of the injection interval for chronic treatment with lanreotide Autogel.

With regard to this observation, one should be cautious to interpret immediate surgical results in patients pre-treated with lanreotide Autogel. Similar to preoperative octreotide LAR treatment, we suggest postponing the postoperative biochemical evaluation to 3 months after the last injection of lanreotide Autogel (19).

Three patients well controlled on octreotide LAR 20 mg, were individually titrated to the maximum dose of lanreotide Autogel. One patient using octreotide LAR 20 mg was subsequently well-controlled with the lowest dose of lanreotide Autogel, e.g. 60 mg/4 weeks. Thus on an individual basis, different pharmacokinetics, for instance bioavailability, could lead to discrepancies in effective dosing.

In conclusion, lanreotide Autogel and octreotide LAR were equally effective in controlling GH secretion in active acromegaly as measured by suppression of total 24 h GH secretion and by mean GH levels and IGF-I concentrations. Further analysis should be focused on efficacy in the long-term.
Chapter 2

References


Octreotide and lanreotide are equally effective in controlling GH secretion.


