Octreotide treatment in acromegaly: a comparison between pen-treated and pump-treated patients in a cross-over study

Ferdinand Roelfsema, Marijke Frölich, Hans de Boer and Alan G. Harris

Department of Endocrinology, University Hospital, Leiden, The Netherlands, and the Department of Neuroendocrinology, Sandoz Ltd, Clinical Research, Basel, Switzerland

Abstract. The effect of a schedule of three daily injections of 100 μg octreotide (pen treatment) compared with that of a continuous sc infusion of 300 μg/24 h on GH and IGF-I suppression, and other GH-dependent parameters was studied in 10 acromegalic patients in a cross-over study. Treatment was administered via a specially designed pen or a pump for 4 weeks. Following a washout period of a further 4 weeks, patients were switched to the other mode of delivery. Mean GH levels decreased from 26.2±4.7 to 9.9±3.1 mU/l (p=0.007) during pen therapy and to 7.7±2.4 mU/l (p=0.003) during pump treatment. IGF-I levels decreased from 75.6±9.5 to 42.0±9.3 nmol/l (p=0.003) during pen treatment and to 32.5±2.5 nmol/l (p=0.001) during pump treatment. There was a significant difference in IGF-I levels between pen and pump treatments (p=0.03). In 7 patients the IGF-I levels normalized during pump treatment compared with 3 patients in the pen treatment group. There was no change in the free T₄ index levels, but the free T₃ index significantly decreased during therapy, without changes in plasma TSH. This study demonstrates that continuous infusion with octreotide results in a better control of GH oversecretion than the intermittent mode of delivery.

Although the GH-lowering effect of somatostatin was demonstrated shortly after its isolation (1,2), its therapeutic use in GH-excess syndromes became only possible when the long-acting cyclic analogue, octreotide, was developed (3). Intermittent subcutaneous injections of octreotide in patients with active acromegaly inhibit excessive GH secretion and result in improvement in clinical symptoms associated with decrease or normalisation of circulating IGF-I levels (4,5). However, the required daily dose can vary considerably between patients, and doses of up to 1500 μg/day may be necessary (6,7). Since octreotide has a plasma half-time of 113 min after sc injection, GH levels tend to rise after 6-8 hours (8). Therefore, several groups of investigators administered octreotide by continuous sc infusion, and compared its effect with intermittent injections. In these short-term studies sc infusion of octreotide for 2-3 days was more effective in suppressing GH levels than intermittent injections (9,10).

The purpose of the present study was to compare the efficacy of both treatment modalities given long-term. To this effect we have investigated the effect of octreotide administration on GH-levels, as well as on a variety of other parameters, including IGF-I, thyroid hormone levels, glucose tolerance, and insulin levels in a cross-over study.

Patients and methods

Six female and 4 male patients were enrolled in this study. The mean age was 56 years, range 37-72. Five patients had undergone previous treatment: 4 had transsphenoidal surgery, and one transsphenoidal surgery followed by radiotherapy. All subjects had clinical signs of active disease, elevated IGF-I levels, and insufficient suppression of GH by glucose loading. None of the patients had clinical or biochemical evidence of anterior pituitary insufficiency, as tested by specific anterior pituitary tests. Circulating hormone levels of target organs were within the normal limits of reference values for age and sex.
Treatment with dopaminergic drugs was withdrawn at least 6 weeks before the study.

Study design
All patient assessments were performed during hospitalization. The first pretreatment evaluation included an oral glucose tolerance test (OGTT), a 24-h GH profile (samples taken at hourly intervals), and basal levels of IGF-I, T4, T3, T3 resin uptake, TSH, and phosphate. Meals were served at 08.00, 12.30 and 17.30 h. During hospitalization patients were thoroughly instructed in the use of pen and pump.

After 4 weeks of treatment with 300 µg octreotide per day, given as 3 sc injections (at 08.00, 16.00 and 22.00 h) by means of a pen injector (D-pen®, Disetronic, Switzerland) or as chronic sc infusion with a small portable pump (Disetronic, Switzerland), patients were readmitted and the same evaluations were repeated. Treatment was then discontinued for 4 weeks, whereafter the assessments were repeated and patients switched to the other mode of delivery. Assessments were repeated after another 4 weeks while on treatment. Hourly blood samples were taken for the measurement of octreotide throughout the duration of administration of the drug (24 h). Particular attention was paid to possible adverse reactions. At the end of the study, patients were free to choose either mode of treatment long-term. Informed consent was obtained from all patients and the study was approved by the ethical committee of the Leiden University Hospital.

Assays
GH was measured with an RIA (Biolab, Serono, Switzerland), calibrated against WHO-IRP 66/217. The detection limit was 0.3 mU/l. The inter-assay coefficient of variation was <7%. Normal suppression of GH levels during OGTT is <25 mU/l (11). Octreotide levels were measured in the Clinical Research Laboratory of Sandoz (Basle, Switzerland) with a specific RIA. The detection limit of the assay was 0.1 µg/l, the inter-assay coefficient of variation <15%. IGF-I was measured with a RIA (Incast, Stillwater, MN) after extraction and purification. The limit of detection was 1.5 nmol/l, the inter-assay coefficient of variation <11%. Normal values ranged between 9.3-33.2 nmol/l for subjects aged 30-50 years, 8.1-26.5 nmol/l for those aged 50-70 years, and 7.6-17.3 nmol/l for those aged 70 years or more (12,13). TSH was measured with a time-resolved fluorimetric IRMA (Pharmacia, Uppsala, Sweden). The inter-assay coefficient of variation was <6%. Normal basal values for TSH were 0.2-6 mU/l. Insulin levels were measured with an RIA (11). Normal fasting levels were below 15 mU/l and the normal integrated incremental response during OGTT <325 mU/l (11).

Thyroid hormone levels were measured with materials from Abbott (Chicago, IL); T4 with a fluorescence polarization immunoassay (TDX) and T3 with an RIA (T3 RIA bead); T3 resin uptake was determined by measuring the saturation of serum thyroxin (Triobead-125). Plasma phosphate was quantitated in a fully automated system (SMAC, Technicon, Tarrytown, USA).

Statistical analysis and other calculations
Data were analysed by ANOVA for repeated observations and by linear regression. Carry-over effects were assessed according to the method described by Armitage & Hills (14).

The cross-correlation between GH and octreotide series was calculated after ARIMA (autoregressive integrated moving average) modeling of the individual series (15). The residuals were tested statistically for the absence of significant spikes at key lags and a non-significant Q statistic. After appropriate transformations of the series, the cross-correlation coefficients were calculated for statistical significance. With this procedure the influence of autocorrelations is removed so that spurious cross-correlations are no longer present.

Results
Mean GH and IGF-I levels are shown in Table 1. There was no significant difference in mean 24-hour GH levels during the baseline study and the washout period (26.2±4.70 vs 25±4.7 mU/l). During pen therapy mean GH levels decreased to 9.9±3.1 mU/l (p=0.007), and during pump therapy to 7.7±2.4 mU/l (p=0.003). The difference between overall mean GH levels during pump and pen treatment was not significant (p=0.067, Table 2). No carry-over effect could be demonstrated, so that the order of treatment mode had no influence on the results obtained. In 8 patients the mean GH levels were clearly lower during treatment with the pump than during treatment with the pen. When the GH data were expressed as a percentage of the baseline values, the values obtained during treatment with the pump were lower than during pen treatment (35.6±7.7 vs 45.2±10.5%, p=0.022).

Mean octreotide concentrations during therapy were lower (1.91±0.25 µg/l) in pen-treated than in pump-treated patients (2.20±0.29 µg/l) (p=0.046).

During both modes of treatment no significant correlations were found between the circulating octreotide concentrations on the one hand and body weight, absolute and percentage decrease in GH and IGF-I levels, on the other hand.

As expected, octreotide levels fluctuated more during pen treatment than during pump treatment, and this was assessed by calculation of the
Table 1.
Plasma mean GH and IGF-I concentrations.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Baseline GH</th>
<th>Washout GH</th>
<th>Pen GH</th>
<th>Pump GH</th>
<th>IGF-I (mU/l)</th>
<th>Baseline IGF-I</th>
<th>Washout IGF-I</th>
<th>Pen IGF-I</th>
<th>Pump IGF-I</th>
<th>Order of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>female</td>
<td>69</td>
<td>27.8</td>
<td>39.8</td>
<td>27.9</td>
<td>30.2</td>
<td>3.7</td>
<td>17.5</td>
<td>2.0</td>
<td>14.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>male</td>
<td>42</td>
<td>43.3</td>
<td>118.0</td>
<td>36.8</td>
<td>116.0</td>
<td>34.1</td>
<td>108.9</td>
<td>26.4</td>
<td>100.6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>female</td>
<td>66</td>
<td>13.2</td>
<td>92.7</td>
<td>10.1</td>
<td>38.5</td>
<td>7.5</td>
<td>32.1</td>
<td>7.8</td>
<td>40.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>65</td>
<td>19.6</td>
<td>98.7</td>
<td>18.8</td>
<td>50.9</td>
<td>2.0</td>
<td>15.7</td>
<td>1.2</td>
<td>16.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>44</td>
<td>29.8</td>
<td>72.5</td>
<td>35.1</td>
<td>39.4</td>
<td>16.3</td>
<td>35.5</td>
<td>8.5</td>
<td>22.9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>64</td>
<td>3.7</td>
<td>49.3</td>
<td>2.5</td>
<td>34.7</td>
<td>3.1</td>
<td>37.4</td>
<td>2.2</td>
<td>21.8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>male</td>
<td>67</td>
<td>17.7</td>
<td>100.5</td>
<td>18.9</td>
<td>49.6</td>
<td>16.6</td>
<td>68.1</td>
<td>14.6</td>
<td>52.7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>female</td>
<td>39</td>
<td>16.1</td>
<td>30.2</td>
<td>13.7</td>
<td>25.9</td>
<td>6.0</td>
<td>15.0</td>
<td>4.6</td>
<td>12.2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>female</td>
<td>72</td>
<td>50.6</td>
<td>57.9</td>
<td>46.4</td>
<td>36.8</td>
<td>5.7</td>
<td>25.0</td>
<td>2.7</td>
<td>14.8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>male</td>
<td>37</td>
<td>40.0</td>
<td>96.8</td>
<td>40.0</td>
<td>47.0</td>
<td>4.5</td>
<td>45.0</td>
<td>7.5</td>
<td>29.0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

GH levels were calculated as the mean of 24 hourly samples and expressed as mU/l. IGF-I levels represent single fasting levels, expressed as nmol/l. Reference values range from 9.3-33.2 nmol/l for subjects aged 30-50 years, 8.1-26.5 nmol/l for those aged 50-70 years, and 7.6-17.3 nmol/l for those aged 70 years or more. Treatment order 1 means that treatment with the pump preceded treatment with the pen; order 2 indicates the reverse.

fluctuation index FI according to the formula FI=100 × (maximum level -minimum level)/ AUC/24, in which AUC means the calculated area under the curve. In pen-treated patients FI was 306.7±37.8, in pump-treated 134.2±19.9 (p=0.004). During pen treatment GH levels increased when plasma octreotide levels decreased. This was further analysed with cross-correlation techniques (Autobox Plus, AFS, Hatboro, PE). A significant negative correlation (p<0.01), generally at lag=0, was present in all patients during pen treatment, but absent while they were on the pump. IGF-I levels significantly decreased during octreotide therapy, and levels were lower during pump treatment than during pen treatment (p=0.03, Table 2), but no carry-over effect could be demonstrated. There was a significant (linear) regression between basal IGF-I levels and levels during pump treatment (r²=0.522, p=0.018); a similar trend was noted during pen treatment (r²=0.363, p=0.065).

The correlations became significantly larger by applying a quadratic regression: in pump-treated patients r²=0.906 and in pen-treated r²=0.847.

Table 2.
Circulating hormones and other biochemical values before and during octreotide therapy.

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Washout</th>
<th>Washout vs basal</th>
<th>Pen</th>
<th>Pen vs basal</th>
<th>Pump</th>
<th>Pump vs basal</th>
<th>Pump vs pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GH (mU/l)</td>
<td>26.2±4.7</td>
<td>25.0±4.6</td>
<td>NS</td>
<td>9.9±3.1</td>
<td>0.007</td>
<td>7.7±2.4</td>
<td>0.003</td>
<td>0.067</td>
</tr>
<tr>
<td>IGF-I (nmol/l)</td>
<td>75.6±9.5</td>
<td>46.9±8.1</td>
<td>0.005</td>
<td>42.0±9.3</td>
<td>0.003</td>
<td>32.5±8.6</td>
<td>0.000</td>
<td>0.03</td>
</tr>
<tr>
<td>Σ glucose (nmol/l)</td>
<td>37.0±3.4</td>
<td>33.0±4.2</td>
<td>NS</td>
<td>41.5±4.4</td>
<td>NS</td>
<td>47.9±2.5</td>
<td>0.013</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (mU/l)</td>
<td>20.8±3.9</td>
<td>12.3±3.5</td>
<td>0.07</td>
<td>12.7±4.5</td>
<td>0.04</td>
<td>8.3±2.5</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Σ Δ insulin (mU/l)</td>
<td>559±120</td>
<td>526±89</td>
<td>NS</td>
<td>357±159</td>
<td>0.008</td>
<td>408±129</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.30±0.02</td>
<td>1.32±0.05</td>
<td>NS</td>
<td>1.26±0.06</td>
<td>NS</td>
<td>1.14±0.03</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Free T₃ index (nmol/l)</td>
<td>101.7±10.7</td>
<td>109.9±8.3</td>
<td>NS</td>
<td>102.5±10.4</td>
<td>NS</td>
<td>99.1±8.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Free T₃ index (nmol/l)</td>
<td>1.85±0.18</td>
<td>1.76±0.13</td>
<td>NS</td>
<td>1.63±0.14</td>
<td>0.03</td>
<td>1.39±0.10</td>
<td>0.003</td>
<td>0.03</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>0.82±0.39</td>
<td>0.95±0.24</td>
<td>NS</td>
<td>0.88±0.21</td>
<td>NS</td>
<td>0.86±0.17</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SEM. For the analysis of glucose and insulin levels data of the patient with overt diabetes mellitus were excluded.
Such a correlation was not found for pretreatment GH levels and GH levels obtained during therapy.

In contrast to mean GH levels, IGF-I levels during the washout period were lower than during the baseline study \((p=0.005)\) independent of the order of treatment. Normal IGF-I levels with respect to age and sex of the patient were reached in 7 during pump therapy and in only 3 treated with the pen.

The results of the OGTT, excluding the data from the patient with overt diabetes mellitus, are shown in Fig. 1. Integrated glucose levels were higher during treatment with the pump than during the baseline and washout studies. \((p=0.013, \text{Table } 2)\). The insulin response during octreotide treatment was sluggish and the integrated incremental value during pen treatment was significantly lower than during the control studies (Table 2). Fasting insulin levels decreased during octreotide treatment and a similar tendency was noted during the washout period (Table 2). The levels obtained during pen and pump treatment were not significantly different. Unfortunately, \(\text{HbA}\_1\text{c}\) levels were not measured during the baseline study. During treatment these levels were less than 6.5\% in all patients, except in the one with overt diabetes mellitus (maximum value 7.5\%). During the OGTT, GH levels were suppressed below 2.5 mU/l in 5 pen-treated and in 5 pump-treated patients.

Whereas the free \(T_3\) index remained unchanged, the free \(T_4\) index significantly decreased during treatment with either pen or pump. However, the difference between pen and pump treatments was significant \((p=0.03)\), with no carry-over effect.

There were no significant changes in TSH levels. Plasma phosphate significantly decreased during pump treatment only \((p=0.001)\). The most significant adverse reaction noted was the presence of loose stools and abdominal cramps in all patients, which resolved spontaneously after 7-10 days of treatment.

**Discussion**

The present study was designed to compare the efficacy of an intermittent injection schedule with that of continuous sc infusion (CSI) of octreotide. In acute studies GH levels were better controlled by infusion than by injections (9,10). However, these studies did not establish whether this effect is maintained during long-term therapy. In the present study we found lower GH levels during CSI than during the injection schedule in 8 patients, but statistical analysis for the whole group showed only a borderline significant difference between the two modes of administration. However, when the percentage decrease of GH was used in the analysis, a significant difference between the two treatment modalities was found. More important, however, was the finding that circulating IGF-I levels were lower during continuous infusion therapy than during intermittent injections and IGF-I levels normalized in more patients during infusion therapy than during the injection schedule. The decrease of plasma phosphate towards normal levels was also particularly observed during CSI. Therefore, this mode of administration seems to result in a better control of GH overproduction and its resulting levels.
manifestations than intermittent injection schedules.

Plasma levels of octreotide did not correlate with the response of GH and IGF-I to octreotide treatment, indicating that the sensitivity of the adenoma to octreotide is an important factor in determining the ultimate response to the drug.

This phenomenon may be related to the number of somatostatin receptors per cell, the heterogeneity of the adenoma cells, and their receptor status or differences in post-receptor events to somatostatin (16,17). Indeed, several studies have shown that the dose of octreotide should be individually adapted to patients’ needs: some patients may need only 100 μg/day, others up to 1500 μg/day in order to control GH oversecretion (6,18,19). The present study suggests that better control is obtained with CSI, which is important since the drug is rather expensive, and many patients may need it for prolonged periods. It would be tempting to speculate that the better results achieved with the use of CSI compared with those achieved with pen treatment may be due to the (slightly) higher octreotide levels in the first group. However, our data do not seem to support this view.

Our study also suggests that pretreatment IGF-I levels may determine the outcome of therapy. It must be stressed, however, that this result is based on a limited number of patients. Nevertheless, analysis of the raw IGF-I data in 12 patients reported by Quabbe & Plöckinger (6) leads to a similar conclusion ($r^2=0.515$, $p=0.009$).

Plasma TSH concentrations were not influenced by treatment, which is at odds with another study where a moderate decrease in basal TSH was found (5). However, a significant decrease in circulating $T_3$ was noted in the present study, whereas $T_4$ levels remained unchanged. Studies of adults on GH therapy because of GH deficiency as well as in vitro studies demonstrated that GH stimulates 5'-deiodination (20,21).

A transient decrease in circulating $T_3$ in acromegalic patients on octreotide therapy was noted in one acute study (9), but the decrease persisted in only one patient on thyroxin replacement therapy.

Our data, therefore, indicate that effective lowering of GH secretion leads to depressed circulating $T_4$ levels probably caused by diminished extrathyroidal conversion of $T_4$ to $T_3$. The clinical significance of the slightly lowered $T_3$ levels is not clear as yet, but it may explain the absence of the expected lowering of TSH levels during octreotide administration.

The effect of octreotide on glucose tolerance and insulin response is more complex. Insulin release is directly inhibited by octreotide, but on the other hand the decrease of the circulating GH level also leads to diminished release of insulin (11). In addition, glucose absorption is delayed during octreotide therapy, which may contribute to a delayed insulin response (22). In patients on long-term octreotide therapy, it is probable that glucose and insulin dynamics would be better investigated by intravenous glucose loading. Nevertheless, in our study, as well as in many others, no significant disturbance of glucose metabolism was noted, as shown by HbA1C levels during pen and pump treatment.

In summary, this study demonstrates that continuous sc infusion of octreotide inhibits GH oversecretion better than intermittent sc injections. Although mean GH levels during these modalities were comparable, GH-dependent peripheral effects differed according to the mode of treatment, including circulating IGF-I, $T_3$ and phosphate levels.

Acknowledgments

This study was supported in part by Biolab/Serono, Amersfoort, The Netherlands.

Ms N. Bravenboer is a student of health sciences, and helped with the studies. The manuscript was typed by Mrs R. van Zeijl-van Rijn.

References


5. Barkan AL, Kelch RP, Hopwood NJ, Beitins IZ.


Received October 19th, 1990.
Accepted March 6th, 1991.

Dr F. Roelfsema,
Department of Endocrinology,
University Hospital,
Bldg 1, B4-P17,
P. O. Box 9600,
NL-2300 RC Leiden,
The Netherlands.