Short Term Treatment with Different Doses of Human Growth Hormone in Adult Patients with Growth Hormone Deficiency

YUZURU KATO, HONG-YI HU, AND MOTOI SOHMIYA

First Division, Department of Medicine, Shimane Medical University, Izumo 693 Japan

Abstract. We studied the effects of short term replacement with human GH at three doses (0.124, 0.250 and 0.375 IU/kgBW/week) in 12 adult patients with GH deficiency (GHD). The patients were divided at random into three groups of 4 patients (groups A, B and C) and each group was treated with three doses of GH and placebo for 10 weeks in shifts of two weeks each. The replacement was started with one of three doses of GH given sc daily at 2100 h for 2 weeks, which was followed by placebo treatment for 2 weeks. The various doses of GH and placebo were then given alternately. GH treatment increased serum IGF-I and IGF-BP3 levels in all the patients examined although the responses were partly influenced by the order of GH treatment. When the data obtained with the same doses of GH in the three groups were combined, a dose-response was demonstrated. There was a close correlation ($r=0.726$) between serum IGF-I and IGFBP-3. Serum triiodothyronine as well as non-esterified fatty acid (NEFA) levels also increased after GH replacement. Adverse side effects included edema in two cases and sleep distress in one case during the GH treatment at the highest dose of 0.375 IU/kgBW/week. These findings indicate that short term replacement with GH at the doses of 0.125 and 0.250 IU/kgBW/week is safe and effective in adult patients with GHD.

Key words: Adult GH deficiency, IGF-I, IGFBP-3, NEFA, HbA1c

Human GH has been used in the treatment of children with GH-deficiency (GHD) for more than 30 yr since the first report of Raben [1]. The most common dosage of human GH to promote the growth in these children has been considered to be 0.5 IU/kgBW/week, which could be administered daily as a sc injection. Recently, GH treatment has been evaluated in adults with GHD [2–8], which resulted in a number of beneficial effects on body composition, muscle strength, bone formation and general well-being. But, GH treatment at the dose recommended for children resulted in a frequent occurrence of fluid retention in adult GHD [3, 5, 6], suggesting a preferential use of a lower dose in elderly patients [9, 10]. The appropriate dosage and the effective parameters of GH treatment remain to be fully elucidated. In this study, we compared the effects of short term treatment with GH at three doses in 12 adult patients with GHD.

Patients and Methods

Patients

Twelve adult patients with GHD (8 male and 4 female) were studied. They were aged from 22 yr to 64 yr with a mean ± SD of 42.1 ± 15.7 yr. All patients had a peak plasma GH response of less than 5 ng/ml to insulin-induced hypoglycemia and arginine stimulation. GHD was idiopathic in 3
patients and secondary in 9 patients: 2 with pituitary adenoma, 2 with Sheehan’s syndrome, 2 with germinoma after radiation, 2 with hypophysitis and one patient with craniopharyngioma after surgery. All patients were adequately replaced for thyroid, adrenal and posterior pituitary functions. No patient had received GH treatment before entry into the study. Patients with diabetes mellitus were not included in the study, although 5 out of 12 patients showed impaired glucose tolerance (IGT) in a 75 g oral glucose tolerance test before the GH replacement.

All patients were randomly divided into three groups (groups A, B and C), in each of which was composed of 4 patients. The treatment was performed for 10 weeks, divided into 5 periods of 2 weeks. In the first, third and fifth periods, the patients were treated with one of three doses of GH, and in the second and fourth periods they were injected with the same volume of placebo (vehicle solution). Group A patients were treated with GH in the order of 0.125, 0.250 and 0.375 IU/kgBW/week. Groups B and C were injected with GH in the order of 0.250, 0.375 and 0.125 IU/kgBW/week, and 0.375, 0.125 and 0.250 IU/kgBW/week, respectively.

Informed consent was obtained from each patient before participation in the study. The study design was approved by the Ethical Committee on Clinical Research in our institute.

Drugs

Recombinant human GH (Genotropin) and placebo were kindly provided by Pharmacia Co. (Stockholm, Sweden) and Sumitomo Pharmaceutical Co. (Tokyo, Japan). The preparation contained either 16 IU/ml of recombinant human GH in a vial or the same volume of vehicle solution as a placebo. They were injected sc by each patient daily at 2100 h according to the examiner’s instructions. The patient could not distinguish the content of each vial throughout the study.

Study design

Blood samples were collected during fasting in the morning immediately before, and 2, 4, 6, 8 and 10 weeks after starting the study. Urine samples were also collected for 24 h on the same schedule. Urinary GH levels were measured by EIA as described previously [11]. Serum insulin-like growth factor I (IGF-I) was measured by specific RIA as reported previously [12]. Serum IGF-binding protein 3 (IGFBP-3) was measured by immunoradiometric assay (IRMA) with a commercial kit (Diagnostic Systems Lab., Webster, U.S.A.) [13]. Biochemical parameters including serum total cholesterol, non-esterified fatty acids (NEFA), triglyceride, alkaline phosphatase, urea

Table 1. Clinical characteristics of 12 adult patients with GHD treated with human GH

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex (F/M)</th>
<th>BW (kg)</th>
<th>Etiology</th>
<th>75gGTT</th>
<th>Replacement with GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>61</td>
<td>Pituitary adenoma</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>M</td>
<td>55</td>
<td>Hypophysitis</td>
<td>N</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>M</td>
<td>54</td>
<td>Hypophysitis</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>F</td>
<td>45</td>
<td>Sheehan’s syndrome</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>46</td>
<td>Idiopathic</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>F</td>
<td>80</td>
<td>Germinoma</td>
<td>N</td>
<td>B</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>74</td>
<td>Pituitary adenoma</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>M</td>
<td>46</td>
<td>Idiopathic</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>F</td>
<td>44</td>
<td>Sheehan’s syndrome</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>F</td>
<td>45</td>
<td>Idiopathic</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>M</td>
<td>86</td>
<td>Germinoma</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>M</td>
<td>58</td>
<td>Craniopharyngioma</td>
<td>N</td>
<td>B</td>
</tr>
</tbody>
</table>

75gGTT: N, normal; I, impaired. GH replacement was scheduled in order as follows: Group A, 0.125, 0.250 and 0.375 IU/kgBW/week; Group B, 0.250, 0.375 and 0.125 IU/kgBW/week; Group C, 0.375, 0.125 and 0.250 IU/kgBW/week. GH treatment was intermittent and replaced by a placebo injection every two weeks.
GH TREATMENT IN ADULT GHD

nitrogen (BUN), electrolytes, plasma glucose and glycosylated hemoglobin (HbA1c) were measured by conventional methods. Serum triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) levels were also determined as reported previously [14]. Blood pressure, routine urinalysis and circulating blood cell counts (CBC) were also measured every two weeks.

Statistical analysis

Statistical analysis was performed by Friedman test and Scheffe's test. In order to evaluate the effect of GH therapy at different doses, we combined data obtained with the same dose of GH or a placebo in different groups. P values less than 0.05 were considered significant.

Results

Baseline serum IGF-I levels were ranged from 19 to 101 ng/ml with a mean (± SEM) value of 54.6 ± 7.6 in 12 adult patients with GHD. Baseline serum IGFBP-3 levels were ranged from 1.4 to 2.4 µg/ml with a mean (± SEM) of 1.8 ± 0.3 µg/ml in these patients. There was no statistical difference in the baseline levels of serum IGF-I and IGFBP-3 among the three groups.

Figure 1 shows the mean ± SEM values for serum IGF-I and IGFBP-3 in all the three groups of patients treated with GH or a placebo for 10 weeks. As shown by the solid line, serum IGF-I increased in all the three groups of patients after treatment with GH at three different doses for two weeks. As shown by the dotted line in Fig. 1, serum IGFBP-3 also increased after treatment with three different doses of GH in three groups of patients. In group A, the mean serum IGF-I and IGFBP-3 levels seemed to increase in a dose-related manner after treatment with three increasing doses of GH, whereas the effect of the lowest dose of GH treatment on serum IGF-I and IGFBP-3 was rather modified by the preceding higher doses of GH in groups B and C, suggesting that the effect of GH treatment was not completely eliminated during the following two weeks of placebo injection.

When these data obtained with the same doses of GH in the three groups were combined and the effect of the preceding dose of GH was corrected by the difference between the placebo and base-

line, the dose-responses were clear, as shown in Fig. 2.

As shown in Fig. 3, serum IGF-I levels were well correlated to serum IGFBP-3 (r=0.726, P<0.005), whereas there was no statistical correlation between serum IGF-I and urinary GH (data not shown).

Serum T3 was also increased but neither serum T4 nor TSH was changed (Table 2). Serum NEFA was increased by GH treatment but there was no considerable change in serum total cholesterol or triglyceride (Table 2). Fasting plasma glucose slightly increased after GH treatment but remained within the normal range. HbA1c increased consid-
erably in 2 of 5 patients with IGT (cases 7 and 8) during the study (5.7 to 6.3% and 5.8 to 6.4%, respectively). There was no considerable change in serum urea nitrogen (BUN), phosphate or alkaline phosphatase as a result of two weeks of GH treatment (Table 3). Blood pressure, CBC and urinalysis were not changed throughout the study.

Adverse events during the GH treatment included edema in two patients (cases 4 and 9) and sleep distress in one patient (case 4), both of which appeared during the treatment with the largest dose of GH and disappeared spontaneously within two weeks.

Discussion

Adult patients with GHD have been recently treated with human GH [2–8]. A number of bene-

![Fig. 2. Mean (±SEM) serum IGF-I (top panel), IGFBP-3 (middle) and urine GH values (bottom) in 12 patients with GHD before and after two weeks treatment with three different doses of GH. The patients were divided into three groups and treated with one of three doses of GH, 0.125 (L), 0.250 (M) and 0.375 (H) IU/kgBW/week, and a placebo alternately every 2 weeks according to three different schedules. Data for three groups treated with the same dose of GH were combined and corrected by the difference between the placebo and baseline values. C indicates the baseline values before GH treatment. * and ** indicate P<0.05 and P<0.01 vs. C, respectively. # indicates P<0.05 vs. L.](#)

![Fig. 3. Correlation between serum IGF-I and IGFBP-3 levels before and after 2 weeks treatment with human GH in 12 adult patients with GHD.](#)

Table 2. Serum T<sub>3</sub>, T<sub>4</sub>, NEFA, total cholesterol (T-Chol) and plasma glucose levels before and after 2 weeks of GH treatment at three doses and placebo in 12 adult patients with GHD

<table>
<thead>
<tr>
<th>GH injected (IU/kgBW/week)</th>
<th>n</th>
<th>T&lt;sub&gt;3&lt;/sub&gt; (ng/dl)</th>
<th>T&lt;sub&gt;4&lt;/sub&gt; (µg/dl)</th>
<th>NEFA (µEq/L)</th>
<th>T-Chol (mg/dl)</th>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12</td>
<td>99.9 ± 4.8</td>
<td>6.9 ± 0.5</td>
<td>0.26 ± 0.04</td>
<td>198 ± 12</td>
<td>87.1 ± 2.8</td>
</tr>
<tr>
<td>0.125</td>
<td>12</td>
<td>120.1 ± 8.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>7.2 ± 0.7</td>
<td>0.47 ± 0.09&lt;sup&gt;**&lt;/sup&gt;</td>
<td>201 ± 8</td>
<td>91.8 ± 3.1</td>
</tr>
<tr>
<td>0.250</td>
<td>12</td>
<td>121.1 ± 6.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>7.1 ± 0.1</td>
<td>0.72 ± 0.16&lt;sup&gt;*&lt;/sup&gt;</td>
<td>203 ± 9</td>
<td>92.0 ± 3.1</td>
</tr>
<tr>
<td>0.375</td>
<td>12</td>
<td>116.0 ± 8.0</td>
<td>7.1 ± 0.6</td>
<td>0.62 ± 0.16&lt;sup&gt;**&lt;/sup&gt;</td>
<td>196 ± 8</td>
<td>93.3 ± 3.1</td>
</tr>
</tbody>
</table>

Mean ± SEM are shown. * and ** indicate P<0.05 and P<0.025 vs. baseline, respectively.
GH TREATMENT IN ADULT GHD

Table 3. Serum urea nitrogen (BUN), phosphate and alkaline phosphatase concentrations before and after 2 weeks of GH treatment at three doses and placebo in 12 adult patients with GHD

<table>
<thead>
<tr>
<th>GH injected (IU/kgBW/week)</th>
<th>n</th>
<th>BUN (mg/ml)</th>
<th>Phosphate (mg/dl)</th>
<th>Alkaline phosphatase (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12</td>
<td>18.8 ± 1.6</td>
<td>3.63 ± 0.12</td>
<td>57.9 ± 4.7</td>
</tr>
<tr>
<td>0.125</td>
<td>12</td>
<td>17.7 ± 1.5</td>
<td>4.23 ± 0.30</td>
<td>72.4 ± 4.3*</td>
</tr>
<tr>
<td>0.250</td>
<td>12</td>
<td>16.7 ± 0.9</td>
<td>4.00 ± 0.20</td>
<td>67.2 ± 4.3</td>
</tr>
<tr>
<td>0.375</td>
<td>12</td>
<td>17.8 ± 1.3</td>
<td>4.58 ± 0.55</td>
<td>64.7 ± 4.1</td>
</tr>
</tbody>
</table>

Mean ± SEM are shown. * indicates P<0.05 vs. baseline.

Beneficial effects on body composition, muscle strength, bone formation and general well-being have been reported. In these studies, human GH was initially replaced at a similar dose of 0.3 to 0.5 IU/kgBW/week to the dosage recommended for children, which resulted in a relative high incidence of fluid retention as a major problem [2, 4, 5]. GH administration at the lower doses effectively increased serum IGF-I in elderly healthy people [9] and seems to be sufficient to normalize adult GHD [10].

In the present study, we evaluated two weeks of treatment with three doses of GH (0.125, 0.250 and 0.375 IU/kg/week) in 12 adult patients with GHD. We have demonstrated that short term GH treatment of adult GHD with lower doses (0.125 and 0.250 IU/kgBW/week) is sufficient to raise serum IGF-I to within the normal range, which was determined by considering sex, age and body mass index (BMI) as previously reported [10, 15]. There was a positive correlation between serum IGF-I and IGFBP-3. These findings support previous reports indicating that synthesis of IGFBP-3 depends on GH secretion [10, 13], indicating that serum IGFBP-3 as well as serum IGF-I is a good indicator of early response to GH treatment in adult GHD.

Urine GH was also increased by GH treatment in a dose-related manner, but there was no correlation between serum IGF-I and urine GH, indicating that urine GH could be a simple indicator of compliance of GH injection in these patients in heterogenous age groups, since the relationship between circulating GH levels and urinary GH excretion is affected by aging [111].

The lipolytic effect of GH is well known [16]. Treatment with GH has been reported to decrease plasma total cholesterol in normal subjects [17] and adult patients with GHD [3, 18, 19], suggesting a beneficial long-term effect on cardiovascular morbidity [20]. In the present study, we failed to find any lowering of circulating total cholesterol, but confirmed an increase in NEFA levels after a short period of GH treatment [10]. GH treatment may have both a dose dependent effect and a time dependent effect on lipid metabolism.

It was previously reported that short term administration of GH impaired oral glucose tolerance in elderly healthy subjects [9] and plasma glucose increased after GH treatment in adult GHD [3]. In the present study, fasting plasma glucose was slightly increased by the GH treatment and remained within the normal range, but HbA1c increased to above the normal range in 2 elderly patients, both of which had shown an IGT pattern before the GH treatment. It is therefore noted that the diabetogenic effect should be carefully considered in treating elderly GHD with IGT.

It was reported that plasma phosphate and calcium levels increased over baseline values, while plasma urea nitrogen (BUN) and potassium levels decreased in healthy adults after a week of GH administration [9] and in adult patients with GHD after 6 months of GH treatment [3]. But, these parameters were not significantly changed after 2 weeks of GH treatment at lower doses in the present study.

Our findings indicating that serum triiodothyronine increased as early as 2 weeks after the GH treatment are on the same line as previous reports obtained with 4 to 6 weeks of GH treatment [3, 6], suggesting possible rapid conversion of thyroxine to triiodothyronine [21].

Edema was found in two patients during the GH treatment at the highest dose of 0.375 IU/kgBW/week, but the same patients had no edema at lower doses of GH. The side effect was a major problem in GH treatment in adult GHD and more
frequently reported in previous studies with a higher dose of GH [3, 5, 6]. It may be explained by the antinatriuretic effect of GH [22, 23]. Chronic treatment with GH in adult GHD could therefore be considered at the minimal effective dose in the absence of side effects.

In conclusion, the present findings indicate that GH replacement at a dose of 0.125–0.250 IU/kgBW/week effectively increased serum IGF-I and IGFBP-3, sensitive biological parameters of GH action, after a short period of 2 weeks and could be useful for a longer period treatment in adult GHD.

Acknowledgments

We are indebted to Pharmacia Co. and Sumitomo Pharmaceutical Co. for supplying human GH and for cooperation in this study. We also thank Mrs. Akemi Kageyama and Mrs. Akiko Kawakami for technical help and secretarial assistance, respectively. This study was supported in part by grants from the Ministry of Education, Science, Sports and Culture, Japan, and the Ministry of Health and Welfare, Japan.

References


