Two Weeks of Daily Injections and Continuous Infusion of Recombinant Human Growth Hormone (GH) in GH-Deficient Adults: I. Effects on Insulin-Like Growth Factor-I (IGF-I), GH and IGF Binding Proteins, and Glucose Homeostasis

Jan-Ove Johansson, Jan Oscarsson, Ragnar Bjarnason, and Bengt-Åke Bengtsson

Recombinant human growth hormone (GH) is routinely administered as daily subcutaneous injections to patients with GH deficiency (GHD). However, in the hypophysectomized rat, pulsatile and continuous infusion of GH has been shown to differ in terms of the magnitude of effect on longitudinal bone growth, serum insulin-like growth factor-I (IGF-I) concentrations, and hepatic metabolism. The aim of the present study was to compare the effects of daily injections and continuous infusion of GH in GHD adults on previously well-documented GH-dependent factors. Recombinant human GH (0.25 U/kg/wk) was administered to nine men with GHD for 14 days in two different ways, ie, as a daily subcutaneous injection at 8 PM and as a continuous subcutaneous infusion, with 1 month of washout between treatments. Blood samples and tests were performed in the morning after an overnight fast before the start of GH treatment (day 0) and on day 2 and day 14 of treatment. An oral glucose tolerance test (OGTT) was performed on day 0 and day 14. Daily injections and continuous infusion of GH exerted similar effects in terms of body weight and body composition. The two modes of administration resulted in similar daily urinary GH excretion and similar serum GH concentrations in the morning. GH binding protein (GHBP) concentrations did not change significantly during the various treatment periods. Serum IGF-I and IGF-I binding protein (IGFBP)-3 concentrations increased to a greater degree during continuous infusion of GH versus daily injections. Serum IGFBP-I concentrations decreased to a similar degree during the two modes of administration. Serum concentrations of free triiodothyronine and total triiodothyronine (T_3) increased and free thyroxine (T_4) decreased to a similar degree, independent of the mode of administration. However, total T_4 concentrations were unchanged during both modes of treatment. Serum thyrotropin (TSH) concentrations decreased during continuous infusion, and there was a similar nonsignificant decrease during daily injections of GH. Fasting free fatty acid (FFA) levels increased during treatment with one daily injection of GH, but there was no significant effect from continuous infusion. Results of measurements of fasting concentrations of blood glucose and oral glucose tolerance (OGT) indicated a more impaired glucose tolerance after daily injections of GH versus continuous infusion. In conclusion, continuous infusion and daily injections of GH have similar effects on the variables described, but the magnitude of the effects differs.

IN MAN, the secretory pattern of growth hormone (GH) has been shown to be influenced by a number of physiologic and pathophysiologic conditions. Women have a higher mean integrated GH secretion and higher mean baseline GH level than men.[1,2] In pregnancy, the GH secretory pattern becomes more continuous with higher basal levels from the beginning of the second trimester.[3] Moreover, an increase in basal GH levels has been observed during fasting[4] and in poorly controlled diabetes mellitus.[5] Thus, changes in basal GH concentration may cause metabolic adjustments during these states. In the hypophysectomized rat, it has been shown that intermittent administration and continuous infusion of GH differ in terms of the magnitude of effect on longitudinal bone growth, body weight gain,[6,7] serum insulin-like growth factor-I (IGF-I) concentration,[8] and IGF-I mRNA levels in various tissues,[9,10] as well as on hepatic metabolism.[11,12] In all these studies, GH was given for several days.

In children with GH deficiency (GHD), an improved long-term linear growth response is obtained when GH is administered as daily subcutaneous injections versus intramuscular injections two to three times weekly.[13] In adults with GHD, it has been shown that the increase in serum IGF-I is less stimulated by a few intravenous GH pulses per day versus more frequent pulses per day or continuous administration.[14,15] However, in these studies GH treatment lasted only 24 hours.

There are therefore few studies of the metabolic effects during prolonged treatment of GH-deficient adults with different modes of GH administration. We therefore compared 14 days of conventional daily subcutaneous injections in the evening with continuous subcutaneous infusion of GH on previously well-documented GH-dependent factors: IGF-I, IGF binding protein-1 (IGFBP-1) and IGFBP-3, GH binding protein (GHBP), thyroid hormones, and glucose homeostasis.

SUBJECTS AND METHODS

Subjects

Nine men aged 41 to 63 years who had previously been investigated as inpatients at the Endocrine Unit because of pituitary disorders were asked to participate in the study. After insulin (0.1 U/kg body weight)-induced hypoglycemia with blood glucose less than 2.2 mmol/L, they all had serum GH concentrations less than 5 mU/L[16] (Table 1). Two subjects had isolated GHD and seven had multiple pituitary deficiencies that had been present for at least 1 year before the study (Table 1). The patients were on stable replacement therapy with glucocorticoids (cortisone acetate 25 mg/d), L-thyroxine ([L-T_4] 0.10 to 0.15 mg/d), and testosterone enanthate (Table 1). Administration of intramuscular injections of testosterone enanthate was changed 1 month before the study from 250 mg/mo to 125 mg every second week to avoid major changes in

From the Research Centre for Endocrinology and Metabolism, Department of Medicine, Sahlgrenska University Hospital, Göteborg University, Göteborg, Sweden.

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Address reprint requests to Jan-Ove Johansson, MD, Research Centre for Endocrinology and Metabolism, Division of Endocrinology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.

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Table 1. Individual Data on GH-Deficient Men Included in the Study

Patient No.	BMI (kg/m²)	Age (yr)	Diagnosis	Duration of GH Deficiency (yr)	Serum IGF-I (μg/L)†	Maximum Serum GH Response After ITT (mU/L)‡	Hormonal Therapy
1	30.8	47	Chromophobic A	9	114	4.2	LT_4
2	29.6	43	Idiopathic*	3	122	0.3	LT_4, antidiuretic hormone
3	26.1	45	Chromophobic A	5	68	0	LT_4, cortisone, testosterone
4	26.3	47	Chromophobic A	11	96	0.4	LT_4, cortisone, testosterone
5	26.0	41	Chromophobic A	2	122	1.9	—
6	23.8	63	Chromophobic A	10	58	0	LT_4, testosterone
7	28.8	49	Chromophobic A	4	138	0.9	LT_4, testosterone
8	32.6	41	Prolactinoma	2	193	2.5	Testosterone
9	25.6	49	Chromophobic A	2	181	3.1	—

Abbreviations: A, adenoma; ITT, insulin tolerance test; BMI, body mass index.

*Enlarged and thick fibrous dura mater.

†Serum IGF-I concentration before the start of the study.

‡0.1 U insulin/kg body weight.

serum testosterone concentrations during the study period. Subjects on testosterone therapy had a serum testosterone concentration of 16.8 ± 1.6 and 17.2 ± 4.1 nmol/L before the start of the first and second GH treatment period, respectively. Corresponding concentrations for subjects not receiving testosterone therapy were 14.0 ± 2.3 and 14.1 ± 2.2 nmol/L.

Subjects were given recombinant human GH (rhGH; Genotropin; Pharmacia, Stockholm, Sweden) 0.25 U/kg/wk for 14 days in two different ways with a 1-month washout period between the treatment regimens. During the first treatment period, rhGH was administered as a daily subcutaneous injection at 8 PM (KabiPen 16; Pharmacia). During the second treatment period, rhGH was given in the same dose but as a continuous subcutaneous infusion using a MiniMed 404-SP infusion pump (MiniMed Technologies, Sylmar, CA) and a Cliniset Micro Infusion Set (Pharma-Plast, Lynge, Denmark). The needle was inserted 0.1 m from the umbilicus. Body weight was measured to the nearest 0.1 kg and height to the nearest 0.01 m. Blood samples were taken in the morning (7:30 to 9:00 AM) after an overnight fast on day 0, day 2, and day 14. An oral glucose tolerance test (OGTT) with 100 g glucose dissolved in water was performed on day 0 and day 14 starting at 8:00 to 9:00 AM. Venous blood samples were taken for glucose, insulin, and C-peptide determinations at 0, 30, 60, 90, and 120 minutes.

Written informed consent was obtained from all subjects. The study was approved by the Ethics Committee of the Medical Faculty at Göteborg University and by the Swedish Medical Products Agency, Uppsala, Sweden.

Assays

GH concentrations in serum were determined using a polyclonal immunoradiometric assay (IRMA) method (hGH RIA; Pharmacia). Urinary GH level was measured using an IRMA (BioMérieux, Lyon, France). GHBP concentrations in serum were determined using a ligand-mediated immunofunctional assay according to the method of Carlsson et al.[17] One patient was excluded from the analysis of GHBP because heterophilic antibodies to GH interfered with the analysis of GHBP. IGF-I concentrations in serum were determined using a hydrochloric acid–ethanol extraction radioimmunoassay ([RIA] Nichols Institute Diagnostic, San Juan Capistrano, CA). IGFBP-3 concentrations in serum were determined using an RIA (Nichols Institute, Wijehen, The Netherlands). IGFBP-1 concentrations in serum were determined using an IRMA that has no cross-reactivity with other IGFBPs (ACTIVE IGFBP-1; Diagnostic Systems Laboratories, Webster, TX).

Blood glucose concentrations were determined using a glucose dehydrogenase method (Granutest 250; Merck, Darmstadt, Germany). Insulin concentrations in plasma were determined using an RIA (Insulin RIA 100; Kabi Pharmacia Diagnostics, Uppsala, Sweden). C-peptide concentrations in plasma were determined using an RIA (RIA-coat C-Peptid; Byk-Sangtec Diagnostica, Dietzenbach, Germany). Fasting free fatty acid (FFA) concentrations in serum were determined using an enzymatic colorimetric method (NEFAC; Wako, Neuss, Germany).

Serum free T_4 and free triiodothyronine (T_3) concentrations were determined using ligand analog RIAs (Amerlex M; Kodak Clinical Diagnostics, Amersham, Bucks, UK). Total T_4 concentrations were determined using a polyethyleneglycol-assisted single-antibody RIA (Farmos Diagnostica, Turku, Finland), and for total T_3 concentrations, a polyethyleneglycol-assisted double-antibody RIA (Diagnostic Products, Los Angeles, CA). Thyrotropin (TSH) concentrations were determined using an immunoluminometric method (BeriLux hTSH; Hoechst-Behringwerke, Marburg, Germany).

Serum testosterone concentrations were determined using a nonextraction RIA (RSL^{125} testosterone; ICN Biomedicals, Costa Mesa, CA), and serum sex-hormone binding globulin (SHBG) concentrations were determined using an IRMA (Farmos Diagnostica, Oulunsalo, Finland).

Body fat, lean body mass (LBM), and body water were estimated from bioelectrical impedance (BIA-101; RJL System, Detroit, MI).[18]

Statistics

All values are the mean ± SEM. A one-way ANOVA with the complete block design followed by the Student-Neuman-Keul multiple-range test was used to test the effects of GH treatment. Values were transformed to logarithms when appropriate. A P value less than .05 was considered statistically significant.

RESULTS

Serum Concentrations of GH and GHBP and 24-Hour Urine GH Excretion

Morning serum GH concentrations and total 24-hour urine GH excretion were similar during the two modes of treatment. Serum GHBP concentrations did not change significantly during the various treatment periods (Table 2).

Serum Concentrations of IGF-I, IGFBP-3, and IGFBP-1

Serum IGF-I concentrations increased during both modes of treatment, but more markedly during continuous infu-

Table 2. Effects of One Daily Injection (PEN) and Continuous Infusion (PUMP) of GH on GH, GHBP, Thyroid Hormones, Testosterone, and SHBG Concentrations

Treatment	PEN			PUMP		
	Day 0	Day 2	Day 14	Day 0	Day 2	Day 14
S-GH (mU/L)	0.05 ± 0.04	4.6 ± 1.2*	3.7 ± 0.7†	0.20 ± 0.17	6.1 ± 0.4*	5.2 ± 0.4*
U-GH (μU/d)	4.3 ± 0.9	ND	59.1 ± 11.2*	4.3 ± 0.9	ND	57.9 ± 7.1*
S-GHBP (pmol/L)†	224 ± 28	220 ± 31	231 ± 30	192 ± 27	191 ± 31	199 ± 30
S-free T_4 (pmol/L)	14.1 ± 0.9	ND	12.2 ± 0.9*	13.6 ± 0.9	ND	12.0 ± 1.0*
S-T_4 (nmol/L)	101.0 ± 7.3	ND	100.7 ± 8.4	97.1 ± 6.9	ND	95.3 ± 8.8
S-free T_3 (pmol/L)	4.48 ± 0.44	ND	6.16 ± 0.70*	4.23 ± 0.38	ND	5.85 ± 0.54*
S-T_3 (nmol/L)	1.53 ± 0.08	ND	2.21 ± 0.18*	1.48 ± 0.06	ND	1.98 ± 0.10*
S-TSH (mU/L)	0.94 ± 0.37	ND	0.66 ± 0.30	1.15 ± 0.46	ND	0.62 ± 0.27*
S-testosterone (nmol/L)	15.5 ± 1.4	ND	13.0 ± 0.9	15.8 ± 2.4	ND	11.8 ± 1.5
S-SHBG (nmol/L)	24.7 ± 3.9	ND	25.9 ± 4.6	24.9 ± 3.1	ND	23.4 ± 4.0

NOTE. Values are the mean ± SEM of 9 observations.
Abbreviations: S, serum; U, urine; ND, not determined.
*$P < .01$: *v* day 0 corresponding treatment (PEN or PUMP).
†n = 8, since patient no. 8 had heterophilic antibodies to GH.

sion of GH after both 2 and 14 days of treatment (Fig 1A). The increase was 326% ± 38% after 14 days of daily injections of GH and 368% ± 38% after continuous infusion. Similarly, IGFBP-3 concentrations had increased to a greater degree after 14 days of continuous GH infusion (83% ± 13%) versus daily injections (71% ± 12%; Fig 1B). IGFBP-1 decreased significantly during daily injections of GH, and there was a similar but nonsignificant decrease during continuous infusion (Fig 1C).

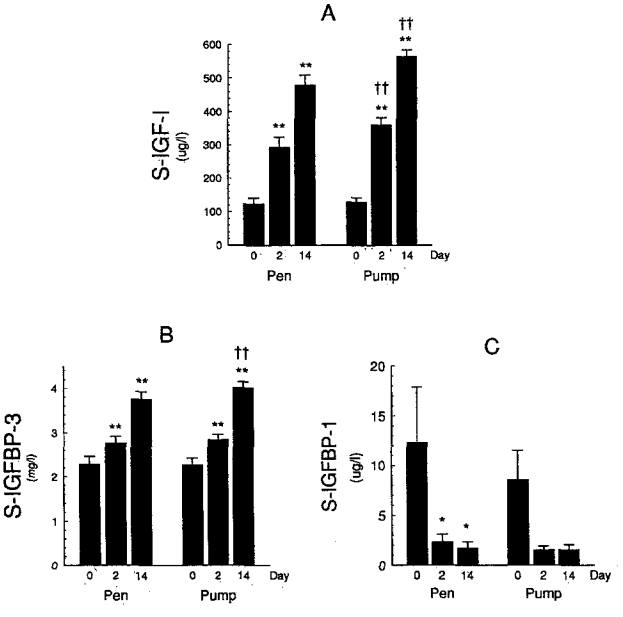

Fig 1. Effects of one daily injection at 8:00 PM (PEN) and continuous infusion (PUMP) of GH on (A) serum IGF-I, (B) serum IGFBP-3, and (C) serum IGFBP-1 concentrations in GH-deficient adults. Values are the mean ± SEM of 9 observations. *$P < .05$ *v* day 0 corresponding treatment (PEN or PUMP); **$P < .01$ *v* day 0 corresponding treatment (PEN or PUMP); ††$P < .01$ *v* the effect of treatment with one daily injection (PEN).

Serum Concentrations of Thyroid Hormones, TSH, Testosterone, and SHBG

Serum free T_4 decreased but total T_4 concentrations were unchanged during both modes of GH treatment. Serum free and total T_3 concentrations increased during both modes of treatment. TSH decreased significantly during continuous infusion of GH, and there was a similar nonsignificant decrease during daily injections. The decrease in serum TSH concentrations was similar when subjects who were not receiving T_4 treatment were excluded (no. 5, 8, and 9; data not shown). Patient no. 3 had no detectable TSH concentration. All patients with a detectable TSH concentration had a decreased serum TSH concentration during both modes of GH treatment. There were no significant differences between the two modes of treatment in terms of serum free T_4, total T_4, free T_3, total T_3, or TSH concentrations (Table 2).

Neither continuous infusion nor daily injections of GH affected serum testosterone or SHBG concentrations (Table 2). This finding was not dependent on whether subjects were receiving testosterone therapy.

Body Weight and Composition

Body weight increased from 93.4 ± 4.6 to 95.1 ± 4.6 kg ($P < .01$) during treatment with daily injections of GH and from 94.0 ± 4.5 to 95.0 ± 4.6 kg ($P < .01$) during continuous infusion. There was no difference between the two modes of administration in terms of body weight gain.

Before daily injections of GH, the proportion of body fat was 22.5% ± 0.9% and that of LBM was 77.5% ± 0.9%. Before continuous administration of GH, the corresponding values were 22.1% ± 0.9% and 77.9% ± 0.9%, respectively. Significant changes in body composition with a decrease in body fat and an increase in LBM and body water were observed after 14 days of continuous GH treatment, and similar changes occurred during daily injections of GH, although they were only significant in the case of body water (Fig 2).

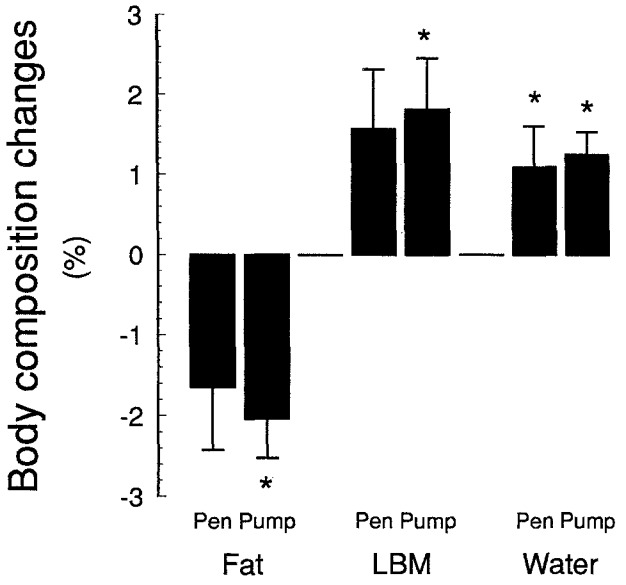

Fig 2. Effects of 14 days of one daily injection at 8:00 PM (PEN) and continuous infusion (PUMP) of GH on percentage changes in body composition, ie, fat, LBM, and water. Body composition was measured using impedance methodology. Values are the mean ± SEM of 9 observations. *P < .05 v day 0 corresponding treatment (PEN or PUMP).

Glucose Homeostasis and Serum Concentrations of FFA

Fasting plasma insulin concentrations increased during 2 and 14 days of treatment during both modes of GH therapy (Fig 3A), as did fasting plasma C-peptide concentrations (Fig 3B). Increases in plasma insulin and C-peptide concentrations were similar for the two modes of treatment. Fasting blood glucose concentrations were normal in all patients both before and after the two modes of GH treatment. The highest individual fasting blood glucose concentration measured before treatment was 5.8 mmol/L, and after treatment, 5.9 mmol/L. Fasting blood glucose concentrations increased during 2 and 14 days of treatment with daily GH injections, but they were not significantly affected by continuous infusion. The increase in fasting blood glucose concentrations was thus more marked after 14 days of daily GH injections (17% ± 4%) versus continuous infusion (11% ± 4%; Fig 3C). Serum FFA concentrations increased during 2 and 14 days of treatment with one daily injection of GH, but did not change significantly during continuous infusion of GH. The increase in FFA concentrations was 73% ± 25% after 14 days of daily injections of GH and 31% ± 13% after continuous infusion (Fig 3D).

To evaluate the effect of GH treatment on glucose

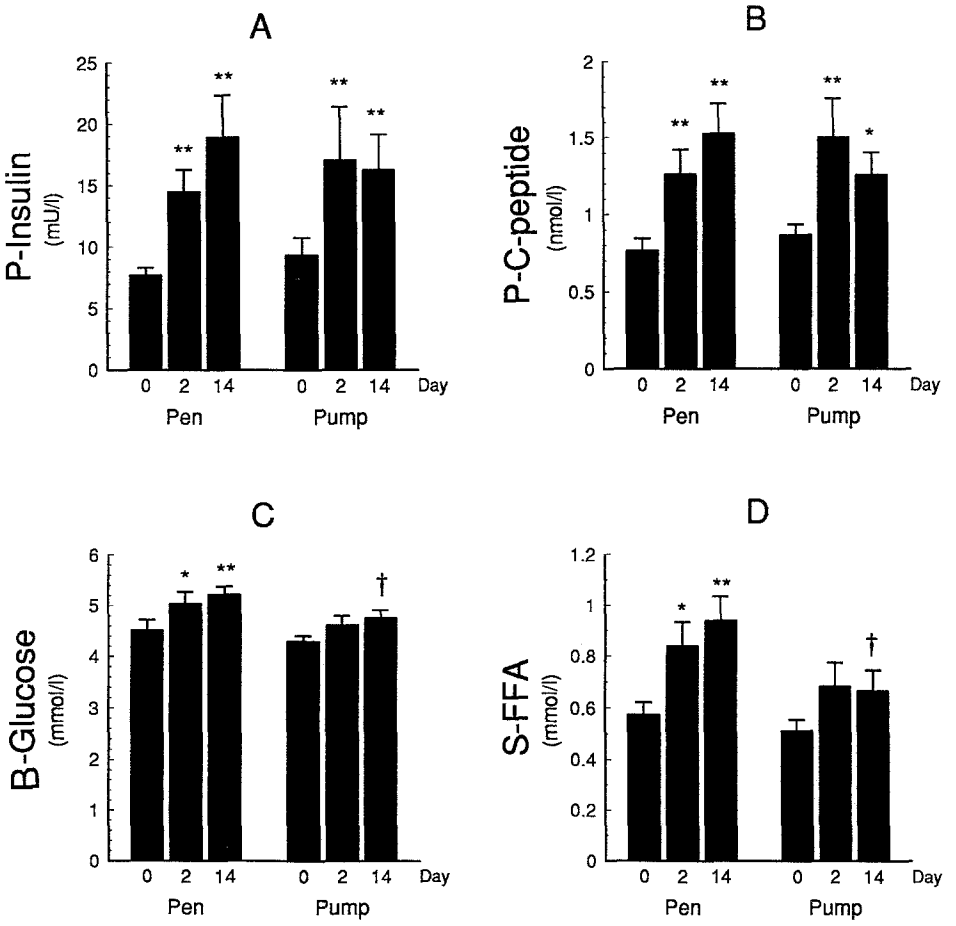

Fig 3. Effects of one daily injection at 8:00 PM (PEN) and continuous infusion (PUMP) of GH on concentrations of (A) plasma (P)-insulin, (B) P-C-peptide, (C) blood (B)-glucose, and (D) serum (S)-FFA after an overnight fast. Values are the mean ± SEM of 9 observations. *P < .05 v day 0 corresponding treatment (PEN or PUMP); **P < .01 v day 0 corresponding treatment (PEN or PUMP); †P < .05 v the effect of treatment with one daily injection (PEN).

Table 3. Effects of One Daily Injection (PEN) and Continuous Infusion (PUMP) of GH on OGT

	PEN		PUMP	
Treatment	Day 0	Day 14	Day 0	Day 14
B-glucose 120 (mmol/L)	4.7 ± 0.5	7.2 ± 0.6†	4.0 ± 0.3	5.5 ± 0.5†§
P-insulin 120 (mU/L)	44 ± 9	152 ± 41†	30 ± 5‡	101 ± 27†‡
P-C-peptide 120 (nmol/L)	3.5 ± 0.4	6.1 ± 0.6†	3.1 ± 0.3	5.0 ± 0.5†§
Sum B-glucose (mmol/L)	25.9 ± 2.1	36.2 ± 2.4†	24.3 ± 1.5	30.4 ± 2.0†§
Sum P-insulin (mU/L)	226 ± 28	634 ± 160†	227 ± 27	538 ± 112†
Sum P-C-peptide (nmol/L)	15.0 ± 1.2	23.9 ± 2.5†	15.0 ± 1.0	21.7 ± 2.1†

NOTE. Values are the mean ± SEM of 9 observations. Patients received 100 g glucose. Blood (B) glucose and plasma (P) insulin and C-peptide concentrations were measured at 0, 30, 60, 90, and 120 minutes. The sum of the values (sum) and values at 120 minutes (120) are given.

*$P < .05$, †$P < .01$: *v* day 0 corresponding treatment (PEN or PUMP).

‡$P < .05$, §$P < .01$: *v* corresponding day during daily GH injections (PEN).

tolerance, an OGTT was performed. Blood glucose, plasma insulin, and C-peptide concentrations at 120 minutes and the sum of values at 0, 30, 60, 90, and 120 minutes were analyzed. Blood glucose concentrations at 120 minutes increased after both modes of GH treatment, but more markedly during daily injections. Similarly, plasma insulin concentrations at 120 minutes increased after both modes of GH treatment and to a higher degree during daily injections, as did plasma C-peptide concentrations at 120 minutes (Table 3). The sum of blood glucose, the sum of plasma insulin, and the sum of plasma C-peptide concentrations increased during the two modes of administration. The sum of blood glucose increased more markedly during daily injections of GH, and the sum of plasma insulin and the sum of plasma C-peptide concentrations increased to a similar degree during the two modes of GH treatment (Table 3).

DISCUSSION

The present study demonstrates that the mode of GH administration affects some but not all of the GH-regulated factors. The increase in serum IGF-I and IGFBP-3 concentrations was more pronounced with a continuous subcutaneous infusion of GH versus daily subcutaneous injections during 14 days of treatment in adults with GHD. Serum IGFBP-1 decreased to a similar degree during the two modes of administration, whereas GHBP concentrations did not change at all. Thyroid hormones and TSH concentrations were similarly affected by the two modes of administration. There were metabolic differences between the two administration modes, including higher fasting FFA concentrations and a more impaired glucose tolerance after 14 days of daily injections versus continuous administration.

All patients received treatment with daily injections during the first treatment period and a continuous infusion during the second period. There was 1 month of washout between treatment periods, and no carryover effects were noted, ie, no difference between baseline values (apart from a lower plasma insulin concentration at 120 minutes before treatment with daily GH injections). It is therefore concluded that the effects of the first treatment period did not influence the effects of the second regimen. Furthermore, urinary excretion of GH was similar during the two different modes of GH administration, indicating that similar total amounts of GH reached the circulation.

A possible explanation for the higher serum IGF-I concentration in subjects given continuous GH could be a diurnal variation in serum IGF-I during daily injections of GH. Diurnal variations in IGF-I concentrations have been observed in GHD patients during 14 days of treatment with daily subcutaneous injections of GH in the evening, with the highest values in the morning.[19] In control experiments, we have observed a similar diurnal variation during treatment of GH-deficient patients with daily injections of GH in the evening. The highest serum IGF-I concentrations were observed between 8:00 AM and noon.[20] Consequently, since all measurements were made in the morning, we conclude that continuous infusion of GH resulted in a significantly higher mean daily serum IGF-I concentration. This finding is in agreement with previous short-term studies (24 hours of GH treatment) of adult patients with GHD, which showed that frequent pulsatile and continuous GH administration induced a greater increase in circulating IGF-I versus a few injections per day.[14,15]

Serum IGFBP-3 concentrations increased in a similar way to IGF-I. IGFBP-3 concentrations thus increased to a greater degree during continuous subcutaneous infusion than during daily injections of GH. This finding is in contrast with previous short-term studies, which were unable to find a difference between intermittent administration and continuous infusion of GH for 24 hours.[15,21] However, direct comparisons between our study and previous studies are difficult to make, since the duration of GH treatment in previous studies was 24 hours and IGFBP-3 concentration starts to increase after about 18 hours of GH treatment.[21]

The circulating level of IGFBP-1 appears to be regulated by insulin and is inversely related to plasma insulin level.[22,23] In adults with GHD, who display decreased insulin production, an increase in IGFBP-1 levels has been found in comparison to healthy controls.[24] The maximum suppression of IGFBP-1, which is mainly dependent on changes in insulin levels, has been shown to occur within 2 days of the start of GH therapy in adults with GHD.[25] The observed decrease in fasting serum IGFBP-1 concentrations during both modes of GH treatment in the present study may therefore be explained by the concomitant increase in plasma insulin concentrations.

We have previously shown that in children with GHD, serum GHBP levels decrease to the maximum degree 90 days after initiation of GH treatment with daily injections. However, this decrease was not observed after 1 year of follow-up study.[26] In contrast, it has been shown that GHBP

concentrations increased during 6 months of GH treatment in prepubertal children with idiopathic GHD. A slight increase was noted during daily injections, whereas continuous infusion of GH resulted in a more marked increase.[27] In the present study, serum GHBP did not change during GH treatment irrespective of the mode of administration. This finding confirms the results of a previous 1-day study.[28] As a result, 14 days of GH treatment may also be too short a time to induce a change in serum GHBP concentrations.

In the rat, liver GH receptors are markedly induced by continuous administration of GH, but not by repeated injections of GH.[10,29] If continuous administration of GH is more effective than single injections for upregulating GH receptors in the liver of adult patients with GHD, this could explain the more marked increase in IGF-I during continuous administration of GH. However, since GHBP is believed to originate from proteolytic cleavage of GH receptors, especially of hepatic origin, the lack of effects of GH treatment on GHBP concentrations in the present study militates against this possibility. Alternative regulatory mechanisms for GHBP are also possible.

The observed GH-induced increase in fasting blood glucose is in agreement with previous findings during long-term GH treatment of adults with GHD.[30,31] The more marked increase in fasting blood glucose during evening injections of GH could be explained by a higher concentration of GH during the night and at dawn,[19,32] which would cause an enhanced insulin-antagonistic effect in the morning.[33-35]

It has previously been shown that continuous subcutaneous infusion of GH for 90 hours in children with GHD impairs oral glucose tolerance (OGT).[36] It is also known that insulin sensitivity, as measured with a hyperinsulinemic-euglycemic clamp, can deteriorate during treatment of GH-deficient adults with daily injections of rhGH.[31] In the present study, the more impaired OGT after daily injections of GH may be explained by a higher serum GH concentration at dawn, since all measurements were made in the morning. Further examination of OGT at other time points would have provided information about diurnal OGT during the two different GH administration modes. An increase in plasma insulin concentrations during GH treatment of adult patients with GHD has previously been noted.[30,31] In the present study, the increase in fasting plasma insulin concentrations was similar during the two GH administration modes. However, after 14 days of daily GH injections, plasma concentrations of insulin and C-peptide had increased to a higher level, although this was not significant. In accordance with the above discussion, a higher serum GH concentration at dawn during daily injections of GH may lead to a more marked increase in fasting blood glucose and a more impaired glucose tolerance, which may in turn lead to increased insulin requirements during this GH administration mode. Alternatively, the more marked increase in serum IGF-I concentrations during continuous infusion of GH may cause a less pronounced increase in plasma insulin and C-peptide concentrations, since IGF-I decreases plasma insulin and C-peptide concentrations dose-dependently during short-term administration.[37-39] Moreover, short-term administration of IGF-I has been shown to have insulin-like effects in healthy humans,[37,38,40] and the more marked increase in serum IGF-I concentrations could thus help to reduce the deterioration in glucose homeostasis during continuous infusion of GH.

GH has a lipolytic action,[41] and FFA levels increase after GH administration both in normal individuals[42] and in patients with GHD.[43] The higher fasting serum FFA concentrations during treatment with one daily injection of GH versus continuous infusion could also be explained by a higher serum concentration of GH during the night and at dawn. A higher GH concentration would cause an enhanced insulin-antagonistic effect[34] and increased lipolysis,[44] which would result in higher serum concentrations of FFA. Since FFAs compete for glucose utilization, as described initially by Randle, et al,[45,46] and increase hepatic glucose production,[47,48] higher concentrations of FFA could contribute to higher concentrations of fasting blood glucose and more impaired glucose tolerance during daily injections of GH. The less pronounced increase in serum FFA concentrations during continuous infusion of GH may also be caused by the more marked increase in IGF-I concentrations, since short-term IGF-I administration has been shown to result in a decrease in FFA concentrations in most studies,[37,38] but not all.[39]

The observed decrease in TSH level during GH treatment of adults with GHD both with and without T_4 substitution is well in agreement with a previous study by Jørgensen et al.[49] The decrease in serum TSH concentrations was only significant during continuous infusion of GH, which may be explained by the nonsignificant reduction in TSH concentration before treatment with daily injections of GH. The decrease in serum free T_4 and the increase in free T_3 and T_3 concentrations during GH treatment of adults with GHD have previously been described.[49,50] Our results extend previous studies by showing that daily injections and continuous administration of GH have similar effects on thyroid hormones.

This study is the first examination of the effects of different GH treatment modes with a duration longer than 1 to 2 days in GH-deficient adults. In conclusion, continuous and daily injections of GH had similar effects on the variables described, but the magnitude of the effects differed. The difference between the two modes of administration may be attributed to different effects on plasma IGF-I and IGFBP-3 levels and/or a higher nighttime serum GH concentration during evening injections of GH. Additional studies are necessary to evaluate which regimen is optimal for long-term GH treatment in GH-deficient adults.

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