Long-term GH treatment of GH-deficient adults: Comparison between one and two daily injections

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ABSTRACT. The physiological pulsatile secretion of GH in humans might be important for the metabolic effects of GH. In the treatment of GH-deficient (GHD) patients, the most common regimen is a single sc injection at bedtime. It has not been completely established if this is the optimal mode of GH administration during long-term GH treatment. The aim of the present study was to evaluate the metabolic effects of two different GH replacement regimens comparing one to two daily injections. Eight men and six women, 42-78 yr old, with verified severe GHD, participated. Patients were matched for gender, age and body mass index (BMI) and were randomized to GH therapy (one or two injections daily) for 12 months. GH doses were individually titrated to IGF-I levels of age-matched controls. IGF-I, glucose, insulin, oral glucose tolerance test (OGTT), cholesterol, triglycerides, lipoproteins, including size fractionation with fast performance liquid chromatography, BMI and body composition were analyzed. After 12 months the median GH dose was 0.45 mg (range 0.25-0.50 mg) in both groups. Body fat had decreased by 20% (p<0.05) in the group receiving one daily GH injection. There were no differences between the two treatment groups in indices of carbohydrate or lipid metabolism. The administration of GH divided into two daily doses offered no major advantage as compared to the more convenient single injection in the evening. The GH-induced reduction in body fat occurred independently from changes in serum lipids.

INTRODUCTION

GH secretion is pulsatile, with the largest pulses at night during sleep (1-3). GH stimulates growth and is important for metabolism, acting either directly or indirectly mediated by IGF-I. Stimulation of growth and production of IGF-I are dependent on the pulsatile secretion of GH (4, 5). To mimic the normal GH-secretion pattern, the most common GH replacement regimen in GH deficient (GHD) patients is a single sc injection at bedtime (6-10). In adults with GHD, previous studies have shown that this type of administration has beneficial effects and is, in addition, well tolerated (8, 11, 12).

GHD is associated with an unfavorable plasma lipid profile with increments in LDL and triglycerides, and several studies have shown that GH replacement decreases LDL levels, while HDL and triglyceride-rich lipoproteins remain unaffected (8, 10-13). However, it is less clear if a single sc injection at bedtime is the most effective administration in terms of metabolic effects. To investigate this, different GH replacement regimens have been evaluated (14-18). Evening vs morning sc injections of GH showed that evening injections were more successful in normalizing metabolism (14). Studies on continuous sc infusion vs one daily sc injection showed similar effects (15-18), as did a study of daily sc injections compared to injections three times per week (19). One short-term study comparing GH injections in the evening to injections twice a day showed a more pronounced increase in IGF-I, but lower night-time levels of lipid intermediates, when GH was injected twice, instead of once daily (17). In these previous studies, GH was administered from 1 to 6 months.

The aim of the present study was to examine whether GH administered to GHD adults during the initial 12

Key-words: Adult GHD, GH-treatment, one or two doses/day, lipid profile.
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Accepted April 28, 2006.
months of replacement, given as one or two doses per day, would give different metabolic effects with special focus on body composition and the plasma lipid profile.

MATERIALS AND METHODS

Patients

Fourteen consecutive patients, 8 men and 6 women, 42-78 yr old, with verified severe GHD, defined by a GH peak response <3 μg/l after stimulation (8), participated. Insulin hypoglycemia, arginin stimulation tests or both (separately) were used. Six patients had been treated for non-secreting pituitary adenoma, three for Cushing’s disease, two had hypophysisis, one prolactinoma, one craniopharyngioma and one had had an apoplexia in the pituitary. The pituitary diseases were diagnosed 2 to 41 yr before GHD was established, and GH replacement started shortly after. Thirteen patients had additional pituitary insufficiencies and had stable conventional replacement therapy with T₄, hydrocortisone and sex steroids. All men were treated with testosterone, whereas three women were treated with estrogens. One woman had isolated GHD. All had adult onset of GHD, and none of the patients had previously been treated with GH.

Experimental protocol

The patients were matched for gender, age and body mass index (BMI) and were randomized for conventional treatment with one sc injection of GH at bedtime (one dose group) or two GH injections per day (two dose group). In the latter group, 1/3 of the daily dose was taken in the morning and 2/3 in the evening, thus, achieving a more continuous GH dose, and at the same time mimicking the physiological secretion pattern (17). The group randomized to GH replacement at bedtime (one dose group) consisted of 4 men and 3 women, 45-77 yr old. The patients randomized to GH replacement in the morning and evening (two-dose group) comprised 4 men and 3 women, 42-78 yr old. The groups did not differ clinically with respect to age, gender, duration of known GHD as well as the number and treatment of other pituitary deficiencies. For both groups, an initial total daily GH dose of 0.15 mg was injected for a month, thereafter doses were individually titrated to achieve IGF-I levels (mean±2 SDS) of healthy subjects. The patients were evaluated and sampled at start, after 6 and 12 months. The Committee for Medical Ethics at the Karolinska Institute approved the study, and all patients consented to study participation prior to sample collection and examinations.

Analysis

Fasting blood samples were obtained in the morning at baseline, after 6 and 12 months and analyzed for IGF-I, IGF binding protein 1 (BP-1), lipoprotein (a) [Lp(a)], 7α-hydroxy-4-cholesten-3-one (C4), cholesterol (total, HDL and LDL) and triglycerides as well as cholesterol and triglyceride lipoprotein profiles obtained from fast performance liquid chromatography (FPLC) separation. IGFBP-1 was measured because of the focus on metabolism in this study.

In the oral glucose tolerance test (OGTT) the patients ingested 75 g glucose dissolved in water. Plasma glucose and serum insulin were measured before ingestion and after 2 h. Impaired glucose tolerance was defined as a 2-h glucose level between 7.8 and 11.0 mmol/l and diabetes as glucose level >11.1 mmol/l. OGTT was performed in the morning at baseline and after 12 months. The homeostasis model assessment (HOMA) index=p-glucose x insulin/22.5 using single fasting sample was calculated as an estimation of insulin resistance (20, 21). We used 2.77 as a threshold for insulin resistance, as suggested in the Bruneck study (22).

Anthropometric methods

Physical examination included measurements of height and weight and BMI was calculated as weight divided by the square of height in meters (kg/m²).

Body fat and lean body mass were determined by dual energy X-ray absorptiometry (DEXA) (Hologic QDR 4500, Hologic, inc., Waltham, MA, USA) according to a standard procedure described earlier (23). Bone mineral density (BMD) of femoral neck and lumbar spine (L2-L4) were assessed with the same instrument. The BMD values in the patients were compared with data from a reference material provided by the manufacturer. The BMD values were expressed as SD scores (SDS) from the mean of young adults (T-scores). The World Health Organization (WHO) definition of osteoporosis and osteopenia was applied; ie BMD between ~1.0 and ~2.5 SDS from the mean of young adults at any measured site was defined as osteopenia. Values <~2.5 SDS were defined as osteoporosis (24).

Assays

IGF-I was determined in serum by RIA (25). Normal range of IGF-I was established from 448 healthy subjects aged 20-96 yr old (26).

IGFBP-1 was analyzed by RIA (27). Reference ranges 7-100 μg/l. Plasma glucose was measured by a standard glucose oxidase method. Insulin was measured by fluoroimmunoassays (autodelfia insulin Wallac O₂, Turku, Finland). Reference value for fasting serum insulin was <20 mU/l. The insulin assay did not cross-react with pro-insulin.

Lp(a) was analyzed with nephelometry (Immage). Normal level was <0.3 mmol/l.

Serum cholesterol and triglycerides were measured with colorimetric methods (Vitos 900) and HDL with direct colorimetry (Hitachi 911). LDL concentration was calculated according to Friedewald’s formula (28).

Plasma lipoprotein profiles as well as cholesterol and triglyceride profiles were also assessed by size fractionation of plasma lipoproteins by a fast performance liquid chromatography system (FPLC), using a micro-FPLC column (30x0.32 cm Superose 68 from Amersham Pharmacia, Uppsala, Sweden) coupled to a system for on-line separation and subsequent detection of cholesterol, as previously described (29). In brief, 10 μl of plasma from each individual were injected into the micro-FPLC system at a flow rate of 40 μl/min.

Specific reagents for cholesterol or triglycerides were purchased from Roche Diagnostics GmbH, Mannheim, Germany.

C₄, which strongly reflects the enzymatic activity of hepatic cholesterol 7α-hydroxylase (CYP7A1) (30-33), was assayed using 1 ml of serum. Samples were diluted with saline, an internal standard [7α-hydroxy-4-cholesten-3-one] was added, and samples were extracted, eluted, dried, and dissolved in acetonitrile as described in detail elsewhere (32). Serum C₄ levels (ng/ml) were also corrected for plasma total cholesterol.