Dose Effects of Growth Hormone during Puberty

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Key Words

Growth hormone · Growth hormone deficiency · Children · Puberty · High dose · Standard dose · Insulin-like growth factor I · Growth velocity

Abstract

During puberty, the production rate of growth hormone (GH) doubles and is associated with an increase in growth velocity. A significant percentage of the final adult height is attained during puberty, then after puberty, the production rate of GH decreases with age. In children with GH deficiency, it is known that the dosage of GH, in addition to the duration of treatment, can greatly influence the final adult height. At present, the dosage of GH given to children of short stature is kept at a constant rate throughout puberty. Thus, a study was conducted to investigate the effects of a higher dose of GH given to GH-deficient children during puberty. In this article, the design and results of the investigation and the importance of the findings will be discussed.

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Introduction

During puberty, the production rate of growth hormone (GH) is approximately doubled [1]. This marked increase in GH production in puberty is an amplitude-

modulated phenomenon as the number of GH peaks (i.e. the pulse frequency) remains approximately the same before, during and after puberty.

The rise in GH output during puberty follows a close temporal relationship with the maximum growth velocity (fig. 1). After the pubertal increase of GH, there is a clear decline in GH production with age. The increase in GH secretory rates is mediated, at least in part, through sex-steroid hormones and can be seen in both testosterone- and oestradiol-treated pre-pubertal children.

Non-aromatizable androgens, such as oxandrolone and dihydrotestosterone, have been shown to have no impact on GH production, while oestrogen receptor blockade with tamoxifen decreases GH production. Conversely, the administration of testosterone increases GH production in boys with constitutional delay of growth and development [3–9]. These data, along with the results from other studies, suggest that oestrogens are the main feedback regulator of the increased GH production observed during puberty [10].

The pubertal growth spurt accounts for around 17% and 12% of the adult male and female height, respectively. This difference between the percentages is largely responsible for the difference in the final height between adult men and women [11, 12]. Several studies in GH-deficient children document a clear impact of the effect of dose, as well as duration of treatment, on final height achieved [13].

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Fig. 1. Results from a cross-sectional study of GH secretion in 60 normal boys during puberty. Concentrations of 24-h mean ($\pm$ SEM) serum GH, as a function of chronological age, are superimposed on the standard growth velocity curve (for the 50th percentile) of North American boys. Reproduced, with permission, from Metzger et al. [2]: © Elsevier, 1994.

Analysis of the physiological GH secretion data during puberty indicates that GH production is much higher during this period than at any other period of life. To date, however, GH dosing during puberty has been kept constant at a dose of around 0.3 mg/kg/week (0.04 mg/kg/day). Thus, a multi-centre study was designed by Mauras and collaborators [10] to determine whether the dose of GH given to GH-deficient patients during puberty, if doubled, would significantly increase the growth rate without causing undue advancement of bone age and, therefore, improve adult height. In this article, the design of this study, the results, and the importance of the findings produced will be discussed.

Study Design

This was a multi-centre, randomized, two-dose study. The demographic and baseline characteristics of the patients studied are shown in table 1. A total of 97 patients participated (83 boys, 14 girls); 42 patients were treated with the standard dose of GH (0.3 mg/kg/week [0.04 mg/kg/day]) and 41 patients with a higher dose of GH (0.7 mg/kg/week [0.10 mg/kg/day]); 14 patients dropped out or were not evaluable. All patients were GH deficient (provocative tests <10 mg/ml GH level) and were at least in Tanner stage 2 puberty. Chronological age and bone age were compatible. All patients were receiving GH for at least 6 months on standard doses before enrolment into the study. Male participants were between 10 and 18 years of age, with a testicular volume of 4 ml or more, and a bone age of 14 years or older. Female participants were

Table 1. Baseline characteristics of patients. Reproduced, with permission, from Mauras et al. [10]: © The Endocrine Society

	Standard dose (0.3 mg/kg/week)	High dose (0.7 mg/kg/week)
Sex, male/female	42/7	41/7
Age, years	14.0	13.7
Bone age, years	13.1	13.1
Tanner stage	3.0	2.9
Maximum stimulated GH, μ g/l	5.7	5.3
Previous GH treatment, years	3.5	4.1
Previous growth rate, cm/year	8.5	8.5
Height SD score	-1.4	-1.2
Predicted adult height SD score	-1.1	-0.9
Mid-parental height SD score	-0.4	-0.3

aged between 8 and 16 years of age, with a Tanner breast stage of 2 or more, and a bone age of 12 years or older. Both groups received GH treatment for a comparable duration of 3.5 ± 2.6 and 4.1 ± 2.9 years. Mid-parental height target score and Bayley-Pinneau-predicted adult height standard deviation (SD) scores were similar (table 1).

Patients were randomly assigned to continue treatment with GH at either dose. Bone age studies were determined every 6 months. Of the 97 participants, 45 were treated for 3 years or more, 48 completed the study and 49 discontinued therapy before completion of the study. Six patients were discontinued as a result of adverse events. The majority of participants discontinued the therapy before the study was completed, however, because they were satisfied with the height they had obtained.

Fig. 2. The effect of dose on the growth rate (mean $\pm$ SD) in the high- and standard-dose groups (* $p < 0.05$). Reproduced, with permission, from Mauras et al. [10]: © The Endocrine Society.

Results

The mean pre-study growth rate was 8.5 cm/year in both groups for patients completing the 12th month of the study. During the study, the mean yearly growth rate was 9.8 cm/year in the high-dose group ($n = 44$) compared with 8.2 cm/year in the standard-dose group ($n = 43$, $p = 0.001$ between groups) (fig. 2).

Data for patients completing 3 years of treatment ($n = 41$), including their height SD scores, are shown in figure 3. The mean change from baseline was 1.4 ± 0.8 in the high-dose group ($n = 22$) compared with 0.9 ± 0.7 in the standard-dose group ($n = 22$, $p = 0.023$ between groups).

The Bayley-Pinneau-predicted adult height is based on height and bone age measurements and increases in accuracy as the adult final height is approached. After 3 years, the standardized Bayley-Pinneau-predicted adult height improved by 1.3 SD (8.4 cm) in the high-dose group ($n = 20$) compared with 0.8 SD (4.8 cm) in the standard-dose group ($n = 20$, $p < 0.032$ between groups). Body mass index did not change significantly in either group (19.3 ± 3.6 kg/m² baseline vs 22 ± 3.6 at 36 months at the standard dose, and 18.3 ± 2.3 vs 22.3 ± 3.2 at the high dose).

There was no significant difference in the cumulative change in bone age between the two groups at 1, 2 or 3

Fig. 3. The effect of dose on the height SD score (mean $\pm$ SD) in the high- and standard-dose groups (* $p < 0.05$). Reproduced, with permission, from Mauras et al. [10]: © The Endocrine Society.

years and there was a mean advancement of approximately 1 year during treatment in both groups. Pubertal progression was also similar in both groups.

Adverse Events

Ten serious adverse events were reported during the study, four in the standard-dose group and six in the high-dose group. Of the serious adverse events, most were considered to be unrelated to GH therapy. One case of worsening scoliosis requiring surgery was reported in each of the high- and standard-dose groups. One case of hip pain in the high-dose group was considered to be possibly related to GH therapy. The other adverse events reported in the standard-dose group were scoliosis and pain in the thigh; the other four adverse events reported in the high-dose group were broadening of the nasal bridge, an increase in shoe size, ankle swelling and pain in the right hip.

Laboratory Data

The concentrations of insulin-like growth factor I (IGF-I) increased, as was expected, but increased to a greater extent in the high-dose group (fig. 4, table 2). In

Fig. 4. The effect of dose on IGF-I SD score (mean $\pm$ SD) in the high- and standard-dose groups. Reproduced, with permission, from Mauras et al. [10]; © The Endocrine Society.

Table 2. Median (range) concentrations of plasma IGF-I (μ g/l). Normal concentrations of IGF-I in children aged between 12 and 16 years: boys, 202–957 μ g/l; girls, 261–1,096 μ g/l

Dose of GH	Baseline	12 months	24 months	36 months	Change in 0–36 months
0.3 mg/kg/week (n = 13)	427 (204–649)	559 (248–851)	651 (121–949)	651 (139–1,079)	208 (–228 to 598)
0.7 mg/kg/week (n = 18)	435 (104–837)	671 (361–1,046)	711 (421–1,285)	910 (910–1,843)	360 (–277 to 1,604)

other laboratory studies, there were generally no significant differences in data between the groups, in particular the levels of glucose, insulin, C-peptide and haemoglobin A1c.

Discussion

The results show a significant increase in growth rate and near-adult height in GH-deficient patients when treated with a high dose of GH for at least 3 years compared with the standard dose. The net increase was an approximate height gain of 4.6 cm in the high-dose group after 3 years of treatment. In patients treated with high-dose GH for 4 years, the net gain was 5.7 cm suggesting that the potential net gain in height increases with years of treatment. Bone maturation progressed at a normal pace.

These data are in stark contrast with the findings reported by Stanhope et al. [14, 15] who treated 52 pre-pubertal children with idiopathic isolated GH deficiency with GH. When the patients reached puberty, they were randomized to receive either GH at a standard dose (approximately 0.2 mg/kg/week [0.03 mg/kg/day]) or a high dose (0.4 mg/kg/week [0.06 mg/kg/day]). The results after 4 years of treatment showed no significant difference in growth rates, but there did appear to be an acceleration of pubertal maturation in boys on the high-dose regimen (fig. 5).

The therapeutic doses were considerably higher in the two groups in the study by Mauras et al. [10] and may explain the encouraging outcome in the final height that was observed. In a recent study, Kamp et al. [16] describe the results of high-dose treatment in patients with idiopathic short stature. The treatment commenced before the onset of puberty and the dose of GH was approxi-

Fig. 5. The effect of GH therapy on the yearly growth rates during puberty in boys with isolated GH deficiency. ns, not significant. Reproduced, with permission, from Stanhope et al. [15]; © S. Karger AG.

mately 0.4 mg/kg/week (0.06 mg/kg/day; mean age, 8.4 ± 1.7 years). High-dose GH treatment accelerated bone age and caused a slightly earlier onset of puberty.

Stanhope et al. [14, 15] and Kamp et al. [16] began the 'high'-dose GH therapy either well before or at the very start of puberty. This difference, in addition to other differences, in the design of the investigations set these studies apart from the Mauras et al. [10] study and may be one of the factors resulting in their poor outcome. In the study by Kamp et al. [16], for example, high-dose GH was already being given to the patients during pre-puberty. It may not be possible, therefore, to 'buy' more height gain earlier, i.e. before puberty. A pharmacologic high dose of GH before puberty may actually stimulate the hypothalamic-pituitary-gonadal axis and thus advance bone age, which would negate any therapeutic effect [17, 18]. This caution may not apply to patients who are small for gestational age and who are given a high-dose GH treatment protocol, as investigators postulate that these patients have a variable degree of GH resistance which, therefore, requires higher GH dosage regimens [19–21].

In summary, increasing the dose of GH before puberty should not be recommended. Children who still have a significant height deficit after they enter puberty and thus have a limited amount of time to benefit from GH treatment may, however, benefit from an increase in the dose of GH.

During a mean of 3 years of therapy, we noticed a significant increase in near-adult height of 4.6 cm in children treated with high-dose GH when compared with children treated with standard GH doses. In children treated for 4 years with high-dose GH, the increase in near-adult height was 5.7 cm. The high-dose therapy with GH appeared to be safe and there was no undue advancement of skeletal maturation. The dosing with GH therapy during puberty was approved by the Food and Drug Administration in the USA in 2000 and may be particularly useful and appropriate for children who are severely growth retarded at the start of or during early puberty. Careful monitoring of the concentrations of IGF-I and IGF-binding protein 3 and continued surveillance for adverse effects is strongly advisable.

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