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EFFECT OF HUMAN GROWTH HORMONE TREATMENT IN CHILDREN WITH GROWTH HORMONE DEFICIENCY, TURNER'S SYNDROME AND ACHONDROPLASIA: A COMPARISON OF DOSE FREQUENCY AND ROUTE OF ADMINISTRATION

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ABSTRACT

Recombinant human growth hormone (hGH) was given for 6 months or longer to 68 patients with GH deficiency, 6 with Turner's syndrome and 5 with achondroplasia, during 1986-1994 in a prospective study.

The total weekly administered dose of GH was 0.6 u/kg. By random sampling, 29 of 68 GH deficient patients (42.6%) received twice weekly (2 iw) intramuscular (im) injections, 17 (25%) received twice weekly subcutaneous (sc) injections and 22 received hGH 6 times per week (6 iw) sc during the first 6 months of therapy.

In the GH deficient group the mean pretreatment height velocity was 4 ± 1.2 cm/yr (mean ±SD). The mean velocity during the first 6 months of treatment was 8.7 ± 2.3 cm/yr ($p<0.0005$), regardless of the frequency and type of GH administration. During the second 6 months and second year of treatment, the mean growth rates were 7.7 ± 2.2 and 6.7 ± 2.2 cm, respectively.

The mean increase in height during the first 6 months of therapy for the 2 iw im group (7.7 ± 1.6 cm) compared with the 2 iw sc group (7.6 ± 2.1) did not exhibit any significant difference ($0.8<p<0.9$).

The comparison of growth velocities after 6 months of therapy using 2 iw sc (7.6 ± 2.1) and 6 iw sc (10.1 ± 3.3 cm/yr) in patients with GH deficiency revealed a statistically significant difference ($p<0.002$).

6 patients with Turner's syndrome aged 4.5 to 15.3 years were also treated with hGH. The mean pretreatment height velocity of 3.6 ± 0.9 cm/yr increased to 6.3 ± 0.8 cm/yr during treatment. 5 patients with achondroplasia aged 3-9.6 years also received hGH for more than 6 months, and height velocity during GH therapy increased compared to that before GH therapy (5.4 ± 1.4 cm/yr vs. 4.7 ± 0.9 cm/yr).

Keywords: Growth hormone deficiency, Turner's syndrome, Achondroplasia

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INTRODUCTION

The advent of recombinant DNA technology has resulted in potentially unlimited supplies of growth hormone. Sufficient growth hormone is now available not only for the treatment of GH deficiency but also potentially for the treatment of other conditions that result in short stature.

Short-term studies have suggested that GH treatment

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may improve the growth rate of subjects with isolated short stature, [3,13] Turner's syndrome[4,11] and chronic renal failure, but long term effects of GH therapy must be investigated. Although human growth hormone has been in clinical use for several years, the problem of optimal dose including frequency and route of administration have not yet been completely solved.[2] Usually, im injections are given twice and thrice weekly, but recent data suggest that daily GH treatment may result in a more substantial increase in growth rate.[1,2] The aim of the present study was to investigate:

1) The effect of GH on the growth of children with growth hormone deficiency, Turner's syndrome and achondroplasia, and

2) To compare the dose frequency (2 iw or 6 iw) and route of administration (im or sc) of hGH in the growth rate of growth hormone-deficient children.

MATERIAL AND METHODS

68 children who had received hGH for at least 6 months are included in the present study. Each patient was measured quarterly for a control year before treatment and the majority for a control year after the treatment.

Growth hormone deficiency was diagnosed by a failure to respond (<12 ng/mL) to two human GH secretagogues (combination of L dopa and propranolol) in two separate tests in a euthyroid child with a growth rate of <4 cm/yr and delayed bone age.

Human GH was measured by RIA using commerical kits (DCP, Los Angeles, CA). The intraassay coefficient of variation was 3.8% for a GH concentration of 2.9 ng/mL (n= 18) and 4.8% for a concentration of 8 ng/mL (n= 12). The interassay coefficients of variation were 5.2%, 4.3% and 3.8% for GH concentrations of 2.9, 7.9 and 11.8 ng/mL, respectively (n= 30).

Cortisol and thyroid hormone deficiencies (if present) were treated in the usual fashion prior to hGH therapy.

Assessment of skeletal maturation was made from x-rays of the left hand and wrist by the method of Greulich and Pyle.[7] Bone age was at least 2 years less than chronologic age in all cases. Height velocity was determined by the difference between two height measurements divided by the time interval between the two measurements in decimal years. For reasons of comparability, data for height velocity have also been expressed as SDS.*

hGH was given 0.6u/kg/wk divided in 2 im doses in 26 patients, 2 sc doses in 17, and 22 children received GH in 6 sc daily doses. All children were seen at 3 month intervals by the same physician.

Evaluation of bone age and GH assays were performed in patients with Turner's syndrome and achondroplasia. Karyotyping was done in girls with Turner's syndrome.

Student's t-test was used for statistical analysis of the data and results are presented as the mean±SD.

*Standard Deviation Scores

$$SDS = \frac{X - \bar{x}}{SD}$$

X= Patient's growth velocity.

$\bar{x}$= mean growth velocity at the revalent age

SD= Standard deviation for growth velocity at that age.

Table I. Growth velocity and growth velocity SDS for age before and 6, 12 and 24 months after GH therapy in 68 patients with GH deficiency.

Time	Growth velocity cm/yr (mean±SD)	Growth velocity SDS for age (mean±SD)
Before treatment	4 ± 1.2*	-0.99 ± 1.78
After 6 months	8.7 ± 2.3*	1.72 ± 2.32
After 12 months	7.7 ± 2.2	0.32 ± 2.41
After 24 months	6.7 ± 2.2	0.29 ± 1.99

*Growth rates whose difference was statistically significant ($p<0.0005$).

Table II. Growth velocity and growth velocity SDS for age before and after GH therapy in 3 groups of patients (Group A= 2 iw im, Group B= 2 iw sc, Group C= 6 iw sc).

Growth velocity cm/year (mean±SD)	Group A (n= 29)	Group B (n= 17)	Group C (n= 22)
Before treatment	4.1 ± 0.5*	3.9 ± 0.7*	3.3 ± 0.9
After 6 months GH therapy	7.7 ± 1.6	7.6 ± 2.1‡	10.1 ± 3.3‡
Growth velocity SDS for age			
Before treatment	-0.92±1.58	-1.39±1.29	-1.09±1.12
After 6 months GH therapy	1.76±2.12	3.74±2.25	5.79±4.42

*Growth rates whose differences were not statistically significant ($0.8 < p < 0.9$).

‡Growth rates whose differences were statistically significant ($p<0.002$).

RESULTS

The mean age of GH deficient children at their first presentation was 5.9 ± 3.2 years, ranging from 1 to 16 years. 39 cases were boys (57.3%) and 29 (42.6%) girls.

Bone age and height age were 3.7 ± 2.1 and 3.1 ± 2.1 respectively. There were 4 affected siblings in the study group.

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The range of peak values of GH (with L dopa and propranolol provocation) was 0.35 to 11.70 ng/mL (4.12 ± 2.51= mean ± SD).

In GH deficient patients the mean pretreament height velocity and growth velocity SDS for age was 4 ± 1.2 cm/yr (mean ± SD) and -0.99 ± 1.78 respectively and the mean velocity and growth velocity SDS during the first 6 months of treatment was 8.7 ± 2.3 cm/yr and 1.72 ± 2.32, respectively ($p<0.0005$), regardless of the frequency and mode of GH administration. During the second 6 months and second year of treatment the mean growth rates were 7.7 ± 2.2 and 6.7 ± 2.2 cm/yr, respectively, which were less than the growth rate during the first 6 months of therapy. Growth velocity and growth velocity SDS for age before and after 6, 12 and 24 months of GH therapy is demonstrated in Table I.

In GH deficient cases, patients who received 2 iw im or 2 iw sc therapy did not exhibit significant differences in growth rates during the first 6 months of therapy.

The mean increase in height for the 2 iw im group and 2 iw sc group was 7.7 ± 1.6 and 7.6 ± 2.1 cm/yr. However, patients who received 6 daily sc injections of hGH were growing significantly more than those who received 2 sc injections of hGH each week (10.1 ± 3.3 cm/yr and 7.6 ± 2.1), ($p<0.002$). The growth velocity and growth velocity SDS for age in patients with three different modes of therapy are shown in Table II.

The age range of 6 patients with Turner's syndrome was 4.5 to 15.3 years (8.6 ± 4.1) with bone age and height age values of 6.5 ± 3.1 and 4.3 ± 1.8, respectively. Karyotypes of 4 of them were 45 XO and 2 had a 45 XO/46 XX pattern. GH response to L dopa and propranolol testing was within the normal range.

The mean pretreatment height velocity of 3.6 ± 0.9 cm/yr increased to 6.3 ± 0.8 cm/yr during treatment.

In 5 patients with achondroplasia aged 3-9.6 years, an increase in height velocity was noted with GH therapy (4.7 ± 0.9 cm/yr vs. 5.4 ± 1.4 cm/yr).

DISCUSSION

Almost 36 years ago, Raben[10] was the first investigator to report the successful treatment of patients with growth hormone deficiency. Such patients were treated with natural GH until awareness of slow virus transmission abruptly ended this practice.[5] The advent of recombinant DNA technology has opened a new frontier in the treatment of growth disorders.

A considerable number of studies on the effect of hGH in growth hormone deficient patients[6,7,13] and patients with other growth disorders have been performed. In the present study the majority of cases with GH deficiency had a substantial improvement in growth rate after commencing GH therapy.

The increase in growth rate was greatest during the first 6 months of therapy. This result was comparable to other reports.[6,8]

A number of studies have been performed to evaluate the effect of sc injection of hGH. All studies conclude that sc injections are as or even more effective than im injections.[1,2,15]

In the present report, interstudy comparison suggests that sc therapy is as effective as im therapy. Whereas twice and thrice weekly injections have been typically advocated, more recent data suggest that daily GH treatment (using the same total weekly dose divided in 6 or 7 daily doses) may result in a more substantial increase in growth rate.[2] This point proved to be correct in the present series.

Turner's syndrome is one of the most frequent chromosomal aberrations. The most frequent stigma is short stature that occurs in nearly 100% of the cases. The etiology of diminished growth rate in girls with Turner's syndrome is not known. The peak serum level of growth hormone after different pharmacological provocation tests has been reported to be normal or elevated in these patients.[12] Since 1960 trials with growth hormone have been carried out in an attempt to promote growth in Turner's syndrome. The growth rate of most of the girls with this syndrome increases during growth hormone treatment.[11,12,13] In the present study the response to GH therapy was impressive.

Turner's syndrome is frequently associated with carbohydrate intolerance.[15] Nevertheless, investigation in these patients did not show any evidence of hyperglycemia.

Achondroplasia is one of the well-known skeletal dysplasias resulting in short stature. Linear growth is severely compromised with relatively short extremities. Final height ranges from 115 to 140 cm in males and 112 to 135 cm in females.[16]

Though the etiology of short stature in achondroplasia seems to be secondary to the bone disorder, an underlying hypothalamic pituitary dysfunction[16] has also been suspected. Yamate et al.[16] studied 22 patients with achondroplasia, and GH response to provocative tests was abnormal in only 5 patients (<20 ng/mL). They treated 18 of these patients with hGH for 6 months. Height velocity significantly increased (4.1 ± 0.8 cm/yr vs. 7.2 ± 1.4 cm/yr).

Patients with achondroplasia in the present study had a normal GH response to provocative tests and administration of hGH caused a significant increase in their growth velocities.

We conclude that:

1) hGH therapy is effective not only in GH deficient subjects, but also in Turner's syndrome and achondroplasia.

2) During the second 6 months period and second year of GH therapy, the growth rate is usually less than that of the first 6 months.

3) sc injection of GH is as effective as im injection in the treatment of GH deficient subjects.

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4) Daily sc injection is the most effective mode of treatment in growth hormone deficient children.

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