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Optimization of Growth Hormone Therapy in Growth Hormone Deficient Children

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Earlier Studies

Successful treatment with human growth hormone (hGH) was initially reported by Raben in 1958[1]. Although it is well established that pituitary derived or biosynthetic hGH increases the growth rate in growth hormone deficient children, many patients that were treated in the early days have not reached their target height, or attained adult height below the third percentile of population standards[2-5]. Several explanation have been suggested for these disappointing results. In the earlier days treatment was started at a rather late age and therefore a substantial growth potential has been lost already. Several investigators found positive correlation between final height, height standard deviation score (SDS) for chronological age (CA) or bone age (BA) and height at the start of treatment, stressing the importance of early diagnosis and treatment to prevent further loss of height[3,4,6].

Another contributing factor might be that GH treatment shortens the duration of puberty and consequently the duration of the pubertal growth spurt. In a recent study in the United Kingdom the pubertal parameters of 134 children with isolated GH deficiency treated with GH were evaluated retrospectively. The duration of puberty was significantly shorter compared with corresponding normal values for girls and boys[7]. Bourguignon and coworkers found a highly significant positive correlation between adult height and the height at the start of pubertal development[8]. Therefore attempts should be made to improve height before puberty starts. When puberty starts while the child is still very short we might consider to give gonadotropin-releasing hormone analogues in addition to GH treatment in order to postpone puberty and thereby improve final height.

In the past, because of the limited supply of pituitary derived GH, the doses of GH and frequencies of administration were low and varied among the various groups in different countries. Some of the earlier results are shown in Table 1. In the Netherlands, the initial weekly dosage of GH was approximately 8 IU divided over two intramuscular (i.m.) injections. All

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TABLE 1. Height Velocities During Growth Hormone Treatment

Author	GH dosage per week		No. of	Height velocity (cm/year, mean (SD)				
	IU	frequency	patients	before	year 1	year 2	year 3	year 4
Trygstad[9] 1968	8-16	1-2	20	2.8	9.7	5.8 (n=13)	5.3 (n=9)	5.0 (n=6)
Tanner[10] 1971	20	2	35	3.1±0.2	9.1±0.5			
Frasier[11] 1977	2.7/m^2 b.s^0	3	12	3.5±0.4	6.4±0.4	4.8±0.4		(n=9)
	5.4/m^2 b.s^0	3	16	3.6±0.4	7.3±0.4	5.8±0.4		(n=14)
Ranke[2] 1979	8-12	2-3	36	3.7±1.1 (n=25)	7.7±2.4 (n=36)	6.0±2.2 (n=33)	5.4±2.2 (n=22)	5.1±2.0 (n=19)
Verbeek[12] 1979	8	2	38	3.1	7.9	6.1	5.0 (n=24)	4.2 (n=12)

^{0} estimated from data given

patients received the same amount of GH irrespective of age, height, weight or body surface[12]. Most studies showed that after an initial period of supra normal growth ("catch-up") with GH therapy, growth velocity settles back to values close to normal for age.

Recent Studies

Therefore, it is reasonable to assume that not only diagnosis and treatment but also optimization of dosage and methods of administration of GH will improve final height. Several groups, in and outside Europe, showed a quantitative relationship between the GH dosage and the growth response to GH replacement[13-16]. However, others questioned such dose-response relationship[17]. Up to the mid-eighties the frequency of two, or three i.m. injections weekly was chosen based on clinical observations of the growth response. It was, however, a compromise between growth rate, the availability of hGH and the amount of GH in each ampoule and cost/benefit calculations. Studies in rats showed the importance for optimal growth with more frequent GH administration[18-20]. Moreover, GH is secreted in episodic bursts over both day and night in normally growing children and therefore at least daily administration appears to be more physiological.

Christiansen and co-workers showed that subcutaneous (s.c.) injections of 2 IU GH per square meter body surface given daily in the evening to GHD children resulted in plasma GH concentrations, which approximated the average nocturnal plasma patterns of normal growing children[21]. Later on it was demonstrated that daily s.c. GH injections instead of twice or thrice weekly i.m. injections resulted in a higher growth rate at least in the first year of study[22,23]. Based upon these findings the currently used treatment schedule for GHD children in the Netherlands in 2 IU hGH/m^2 b.s./day ad-

ministered s.c.

Multi-Centric Dose-Response Study

The availability of an almost unlimited supply of recombinant DNA-synthesized human GH enabled further studies on the dose-response relationship in GH treatment. In 1987 we started a collaborative multi-center dose response study in prepubertal GHD children in the Netherlands. The aims of the study were to assess the efficacy and safety of two different doses of authentic biosynthetic human growth hormone in children with GHD and to compare the effect of two doses GH on clinical, auxological and biochemical parameters. Two groups of prepubertal GHD children with isolated or multiple pituitary b-hGH hormone deficiencies were formed. Group I consisted of patients previously treated with b-hGH for at least one year and for at least half a year on fixed dosage (12IU/m^2 b.s./week s.c.) i.e. transfer patients. Group II consisted of newly diagnosed GHD children. The patients of both groups were randomly assigned to treatment with either 2 IU or 4 IU biosynthetic GH per square metre bodysurface administered s.c. in a daily dosage. For children with multiple pituitary hormone deficiencies adequate replacement doses of thyroxine and/or hydrocortisone were used.

The results of the first two years of study are submitted for publication. The auxological findings can be summarized as follows :

(i) In previously treated prepubertal GHD patients the increase of the GH dosage up to 4 IU/m^2 b.s./day s.c. resulted not only in a renewed catch-up growth in the first year of study but also in a sustained increase in height velocity (HV), HV SDS, height SDS and predicted adult height in the second year significantly higher than with 2 IU/m^2. The advance in bone maturation was comparable for the two dosage groups.

(ii) In newly diagnosed GHD patients one year GH therapy with both 2 IU and 4 IU/m^2/day s.c. resulted in a significant increase in HV, HV SDS and height SDS for CA and BA.

(iii) If not only the GH dosage but also the pretreatment maximal plasma GH value after pharmacological stimulation is taken into account, the higher dosage of 4 IU/m^2 has a significant better effect on the growth response than 2 IU/m^2.

(iv) The change of height SDS for BA compared with pretreatment was significantly higher with 4 IU than with 2 IU GH/m^2 b.s./day. Although these first year results point to a better growth effect with 4 IU than with 2 IU, also in newly diagnosed GHD patients, the second and subsequent years of treatment have to be awaited to draw further conclusions.

CONCLUSION

It is obvious that the results published so far as well as the present preliminary data do not answer many questions regarding the optimal therapeutic regimen in GH deficiency. In particular, long-term follow-up must be organized to evaluate efficacy and safety of GH therapy not only in GHD but also for the "new" indications such as Turner syndrome, short stature without classical GH deficiency and chronic renal failure.

Finally the high expectations and the high costs of longterm GH treatment

should receive full consideration.

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