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DOSE FREQUENCY OF GROWTH HORMONE ADMINISTRATION: TWO YEAR DATA COMPARING DAILY AND THREE TIMES PER WEEK. S. F. Kemp and the National Cooperative Growth Study, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR 97202, and Genentech, Inc., South San Francisco, CA 94080, USA

In the 30 years that growth hormone (GH) has been used to treat GH deficiency, dose frequency has changed considerably. Early studies demonstrated improved response by increasing dose frequency from 2 to 3 times per week (TIW). GH administration in the National Cooperative Growth Study (NCGS) data base changed from 97% TIW 1987 to 85% daily (6–7 injections per week) in 1992. We have calculated growth rates for those naive patients in the NCGS data base with idiopathic growth hormone deficiency who received GH daily (N = 100) or TIW (N = 195). The groups did not differ statistically in terms of age (7.1 yr daily; 6.7 yr TIW), bone age delay (2.1 yr daily; 2.3 years TIW), maximum stimulated GH (5.1 daily; 4.5 ng/ml TIW) or pretreatment growth rate (3.9 cm/yr daily; 4.2 cm/yr TIW). Differences in growth rates for the two groups were most dramatic in the first year of therapy, (daily 11.0 cm vs. TIW 9.4 cm ($p < 0.005$)). Rates remained different in the second year (daily 8.3 cm, TIW 7.5 cm ($p < 0.005$)). Bone age advancement was 1.3 yr (daily) and 1.1 yr (TIW) (ns). Thus, while the advantage of daily over TIW injection frequency is most dramatic during the first year, data from the NCGS show that this advantage continues for at least two years in naive growth hormone deficient patients.

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EXCESS IGFBP-3 PROTEOLYSIS IS PARTLY RESPONSIBLE FOR THE ACCELERATED GROWTH IN CONSTITUTIONALLY TALL CHILDREN

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Serum IGF-I levels in constitutionally tall children and adolescents are above normal on average, but variations between individuals are wide. However these cannot be interpreted without consideration of the IGFBPs, and IGFBP-3 in particular, to which serum IGFs are bound. Recent data from our laboratory indicate that limited proteolysis of IGFBP-3, first described in pregnancy serum, is a physiological mechanism occuring in the normal state, which seems to be essential in controlling IGF bioavailability. Western blot analyses were done of serum IGFBPs in 34 pre-pubertal, constitutionally tall children (1 to 10 years old) using ^{125}I-IGF (ligand blot) and a polyclonal anti-IGFBP-3 antibody with a highly sensitive detection technique (immunoblot). Ligand blotting results were inconsistent. In 60% of cases, IGFBP-3 quantities based on size and density of the 42-39-kDa doublet were appropriate to IGF-I levels, whereas in 40%, they were abnormally low. In the latter, bands of 21.5, 20 and 16 kDa were sometimes detectable, resembling the proteolytic fragments in pregnancy serum. With immunoblotting, the relative amounts of 42-39-kDa doublet were similar to those seen with ligand blotting. In all normal and tall children, a 30-kDa band corresponding to the major proteolytic fragment of IGFBP-3 was present. Its intensity was inversely related to that of the 42-39-kDa doublet. The smaller fragments sometimes seen by ligand blotting were more often detectable by immunoblotting in the tall children. These findings suggest that excess proteolysis of IGFBP-3 which increases the bioavailability of IGF-I (whose levels are generally high) may contribute towards the excessive growth in constitutionally tall children.

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LIPID ABNORMALITIES IN CHILDREN WITH GROWTH HORMONE DEFICIENCY. N.G. Greger, D.C. Postellon, and J.P. Gutai, Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI 48201, USA

The relationship between growth hormone action and lipid metabolism is unclear. Some reports note an increase in total cholesterol levels in patients with growth hormone deficiency but this finding is not consistent between studies. Therefore, this study was designed to evaluate the lipid levels in all children with short stature who were being evaluated for possible growth hormone deficiency with an arginine/glucagon stimulation test. Lipid levels were determined in 110 fasting children and 33 of these children were found to be growth hormone(GH) deficient (but euthyroid).The mean cholesterol values were not significantly different between the control and GH deficient groups (171.8 mg/dl vs. 184.2) however, a distinct bimodal pattern was noted for the GH deficient group with 45% of the levels ≥ 190 as opposed to 26% for the normal short stature group. Hypercholesterolemia (≥ 200) was present in 24% of the GH deficient children. The cholesterol levels did not correlate with the peak growth hormone response or pretreatment growth velocity. This subset of GH deficient children with hypercholesterolemia needs to be characterized further and supports the role of GH in modulating lipid metabolism.

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THREE YEAR EFFICACY RESULTS OF A PLACEBO-CONTROLLED TO DOSE RESPONSE STUDY OF HUMAN GROWTH HORMONE IN TURNER'S SYNDROME. J.J.Chipman, J.H.Holcombe, R.N.Tamura, N.G.Whitaker, K.G.Olovich, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN.

Two hundred thirty-two females with Turner's syndrome, diagnosed by karyotype, were enrolled in this ongoing, age-stratified, double-blinded, randomized, parallel, placebo-controlled (18 months) to dose response study conducted by 50 investigational sites in the United States. Patients were randomized to one of five treatment groups: 0.09 mg/kg thrice weekly with or without daily estrogen, 0.12 mg/kg thrice weekly with or without daily estrogen, or placebo injections with placebo tablets. After 18 months, significant differences (by rank based analysis) were observed between the least responsive treatment group and the remaining four treatment groups for mean change in height, Lyon height standard deviation score (SDS) and growth rate. Additionally, the least responsive treatment group demonstrated a significant ($p<0.01$) increase in 18-month mean Lyon SDS over baseline (+0.14, n=41). Following this initial 18-month period, the least responsive treatment group was reassigned to one of the remaining treatment groups to become a dose response study extended to final height. After 36 months on study, the initial least responsive treatment group (during the first 18 months) remained statistically different from the other treatment groups for mean change in height for the first 36 months. We therefore believe that somatropin with or without estrogen causes a significant increase in growth rate, height, and change in height after 36 months, however the overall effect on final height remains to be quantified. The increase in mean Lyon SDS during the initial 18 months seen for the least responsive treatment group suggests that using Lyon's data as a historical control may over estimate the ultimate effect of growth hormone on final height for U.S. Turner syndrome patients.

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THE EFFECT OF STANOZOLOL ON FINAL HEIGHT AND SKELETAL MATURATION IN TURNER'S SYNDROME. M.Satoh[*1], H.Yano[*1], T.Tanaka[*1], A.Tanae[*2] and I.Ibi[*2], [*1]Endocrine Research Laboratory, National Children's Medical Research Center, [*2]Division of Endocrinology and Metabolism, National Children's Hospital, Tokyo 154, Japan.

<Aims and Methods> The effect of stanozolol on the final height and the skeletal maturation was studied in 35 patients with Turner's syndrome without spontaneous genital bleeding. All patients received stanozolol (1mg/day), estrogen and progesterone therapy. Bone age was evaluated by TW2 RUS method. Height SD score for Japanese Turner standard was used.

<Results> The final height (142.42 ± 3.93cm) was significantly higher than that in untreated group (139.1 ± 5.6cm). △Height SD score (△HSDS) which means the difference between height SD score at the start of stanozolol therapy and final height SD score was 1.00 ± 0.53. There were no significant differences in final height and △HSDS between the patients with 45,X karyotype (n=11) and those with other chromosomal variants (n=24). The final height in SFD group (n=10) was significantly shorter than that in AFD group (n=19). △Bone age/△chronological age ratio during stanozolol therapy in patients whose bone ages were above 12 years old (n=27, 0.31 ± 0.18) was significantly lower than that in patients whose bone ages were below 12 years old (n=7, 1.08 ± 0.23)($p<0.005$).

<Conclusions> Stanozolol didn't accelerate bone maturation after 12 years of bone age. The final height was improved by stanozolol.

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EFFECT ON GROWTH VELOCITY OF DOSE-FREQUENCY OF GROWTH HORMONE (GH) TREATMENT (Rx) IN IDIOPATHIC GH INSUFFICIENCY (IGHD) PREPUBERTAL CHILDREN : THE KABI PHARMACIA INTERNATIONAL GROWTH STUDY (KIGS) EXPERIENCE.

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Growth Velocity (GV) in response to recombinant GH Rx was analyzed using KIGS data base. IGHD was based on classical criteria : short stature, slow growth velocity; GH peak response at 2 provocative tests below 10 ng/ml; thyroid and adrenal status were based on conventional hormonal evaluation (local assays).Organic GHD was ruled out by brain imaging. 1256 prepubertal IGHD GH treated patients in KIGS data base were analysed. At start of Rx median Chronological Age (CA) was 7.3 years, median height Standard Deviation Score (SDS) was - 2.7. Median number of injections was 6/week and medians GV were 8.2 & 6.9 cm/year during Rx year 1 & 2 respectively. Out of ten potential predictors, multiple regression analysis resulted in a five predictors model for growth response to Rx : Target Height (SDS), Height SDS for CA, CA at start, GH Dose & GH injection Frequency (R-square = 0.37).The effect of GH dose at 3 versus 7 injections/week according to CA are shown in the figure. The 2 predictors not shown are fixed at their median value. Conclusions :These data provide useful information for optimizing GH treatment in IGHD and predicting growth response.