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ENDOGENOUS GROWTH HORMONE (GH) SECRETION AND RESPONSE TO METHIONINE-GH THERAPY IN GROWTH RETARDED CHILDREN.

In an open multi-center study 30 short prepubertal children (21 boys, 9 girls) were randomly divided into a treatment group (n=20) and a control group (n=10). Inclusion criteria were: age above 6 years; bone age below 8 "years" for girls and 10 "years" for boys; height SDS <-2.5; growth velocity <P25 for age or bone age; peak plasma GH in standard provocation tests >15 mU/l. In the treatment group endogenous GH-secretion was assessed by a 24-hour GH-profile, arginine infusion, exercise test, GRF (1-29)-test and plasma SM-C/IGF-I. Met-GH was administered s.c. once a day in a dosage of 2 IU/m^2 body surface. The integrated GH concentration over 24 hours (ICGH) ranged between 2.2 and 13.4 mIU/l (median 5.6). In 58% of the children ICGH was <6 mIU/l (3ng/ml), the reported upper limit of "neurosecretory dysfunction". Mean (± SD) growth velocities were:

	Baseline	0 - 3m	3 - 6m	6 - 9m
met-GH	4.4 ± 1.5	8.2 ± 2.3	6.6 ± 2.0	6.5 ± 2.2
control	4.5 ± 0.8	4.4 ± 1.4	3.8 ± 2.1	4.0 ± 1.4

12 Children had a growth response >2 cm/year. There were no significant correlations between the growth response versus ICGH and SM-C/IGF-I. Anti-GH antibodies were positive in 56% of the children at 9 months, in 4 of them with a high binding capacity.

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CONTRIBUTION OF DOSE AND FREQUENCY TO THE THERAPEUTIC EFFECT OF GH.

We treated 42 GH insufficient prepubertal children aged 3-12 years with 12 iu biosynthetic GH per week for 1 year after pretreatment observation of 1 year. Group 1 (n=13) received 4 iu GH 3 days per week, Group 2 (n=21) 2 iu GH 6 days per week and Group 3 (n=8) 1 iu GH twice daily 6 days per week. Between groups, pretreatment age (CA), bone age (BA) and auxological parameters were identical.

Height velocity improved (p<0.001) in all groups with a positive trend in the higher frequency regimens. Changes in height velocity (HV) SDS were +3.8 (sd 1.7) in Grp 1, +5.3 (sd 2.6) in Grp 2 and +5.9 (sd 2.7) in Grp 3. Height for BASDS improved equally in all groups.

Of CA, BA, height SDS, height BASDS, HVSDS, frequency and dose/m^2/wk only pretreatment HVSDS significantly determined response in the 42 children (r=-0.64). A significant difference was observed between the response of children receiving more or less than 15iu/m^2/wk. If children were divided on the basis of pretreatment HVSDS, dose/m^2/wk of GH received within each division affected outcome as follows:-

HVSDS (pre)	>-1		-1 to -2		<-2	
Dose/m^2/wk	<15	>15	<15	>15	<15	>15
Change in HVSDS	+2.1	+3.5	+3.6	+4.2	+5.7	+8.5
s.d.	1.1	0.8	1.4	1.7	2.5	1.9
p		<0.002		NS		<0.03

These data showed that GH dose and frequency of administration are relevant to the response to treatment with GH, but pretreatment HVSDS is the dominant factor in predicting its magnitude.

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TREATMENT WITH RECOMBINANT METHIONYL GROWTH HORMONE OF HYPOPITUITARY PATIENTS PREVIOUSLY TREATED WITH PITUITARY GROWTH HORMONE.

Sixteen patients (15m,1f) with growth hormone (GH) deficiency were treated with methionyl GH (Somatrem, Lilly) for one year after previous therapy with pituitary GH. Mean duration of treatment with pituitary GH was 5,5±3.3 yrs (x±SD), this treatment was interrupted for 0,4 yrs on average before onset of Somatrem therapy. At this time chronological age was 15,1±3,8 yrs, bone age was 12,3±2,7 yrs and height was -2,8±1,1 SD. Somatrem dose was 0,16U/kg i.m. 3 times weekly. The protocol was approved by the ethical committee and informed consent was obtained. Growth velocities during the various periods were: last year on pituitary GH: 7,3±1,9 cm/yr; interval without treatment: 2,3± 0,9 cm/yr; first 6 months on Somatrem: 7,5±1,2 cm/yr; second 6 months on Somatrem: 6,6± 1,9 cm/yr. Bone-age-related growth velocity during Somatrem treatment was high indicating catch up growth even in this advanced age group. Bone age did not proceed unduly during treatment (0,96 "years"/yr). The height deficit decreased from -2,8 to -2,1 SD . There was no indication of glucose intolerance. Mean somatomedin concentrations increased significantly. GH-antibodies demonstrated a slight decrease from onset to 6 months of therapy and no sample was evaluated as positive; however, one patient with allergic diathesis developed increasing titers but continued to grow well. No patient developed significant E.coli polypeptide-antibodies. In conclusion, Somatrem is equipotent to pituitary GH in its growth promoting action. In contrast to the high percentage of GH-antibodies found in previously untreated patients, Somatrem did not induce antibodies in patients pretreated with pituitary GH due to a hitherto unknown mechanism.

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PHARMACOKINETIC PROFILE OF AN I.V. AND S.C. DOSE OF RECOMBINANT HUMAN GROWTH HORMONE.

8 healthy male volunteers aged 21-35 years were given an i.v. dose of recombinant somatropin 0.1 IU/kg BW at 8 a.m. after 12 hours' fasting. Blood was sampled every 5th minute during 2 hours for GH measurements with ELISA. A GH concentration-time curve was constructed for each individual. The curve was biphasic with a half disappearance time of 9.0±3.5 min (mean S.D.) for the α phase measured during the first 60 minutes and 30.7±10.8 min for the β phase between 60-120 min. The metabolic clearance rate varied between 82-139 ml/min/m^2. 8 + 3 volunteers were given the same dose, 0.1 IU/kg BW, s.c. in the morning after 12 hours' fasting. They were resting in bed during the whole experiment, i.e. 12 hours. Lunch and dinner at 5 and 10 hours, respectively. Blood samples every 15 min during the first 6 hours, every 30 min the next 2 hours and every 60 min during the remaining 4 hours. The peak GH Concentration, Cmax, was 53±4.2 mU/l with t_{max} of 5.3±0.6 hours.
After s.c. dosing the serum concentration of GH declined with a half-life of 248±55 min. This half-life, considerably longer than the half-life found after i.v. administration, probably reflects the absorption which thus is the rate limiting step in this way of administration.

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DISPARITY OF PITUITARY AND BIOSYNTHETIC GROWTH HORMONE IN ANTIGENICITY AND GROWTH RESPONSE OBSERVED IN TWO BROTHERS WITH ISOLATED GH DEFICIENCY (IGHD) TYPE IA.

Two boys with IGHD due to GH-N gene deletion developed antibodies (Ab) to exogenous GH. The younger boy A (age 3 y, height -5.8SD at start of R) with high Ab titres did not grow during therapy with pit-GH. After 2 y without R_x and a decrease of Ab titres he showed a tremendous growth response to treatment with bio-methionyl-GH and only a moderate rise of Ab titres. The older boy B (age 9.5 y, height -7.8SD) with low Ab titres showed a normal growth rate during treatment with pit-GH and bio-methionyl-GH.

Growth data & Ab studies(Scatchard analysis with pitGH MRC 66/217)

A GH therapy (U/week)	pit	8-12	no R_x	bio	16	20
duration of R_x(y)		1.8	2.0		0.6	0.6
height velocity (cm/y)		3.3	1.4		14.0	17.3
Ab titres 1 :		$5x10^5$	$2x10^3$		$3x10^4$	$5x10^2$
binding capacity (mg/l)		75	4.4		38.8	1.2
B GH therapy (U/week)	pit	8		bio	12	15	20
duration of R_x(y)		3.0			1.1	0.4	0.6
height velocity (cm/y)		12.4/8.6/7.0			7.6	8.3	9.3
Ab titres 1 :		$2x10^2$			<10	<10	$2x10^2$
binding capacity (mg/l)		0.53			n.d.	n.d.	0.36

Scatchard analysis with bio-methionyl-GH showed a lower binding capacity. This, and the lesser antigenicity of bio-GH may explain the therapeutical success in these 2 patients with IGHD type IA.

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EFFECT OF LHRH ANALOGUE IN PUBERTAL PATIENTS WITH ISOLATED GROWTH HORMONE DEFICIENCY.

In isolated GH deficiency, a too insufficient height at onset of a puberty leads to reduced adult height. In order to prevent this we have tried the efficiency of LHRH analogue in association with GH in such cases.

Long-acting Trp 6 LHRH analogue (LHRHa) was used in 4 male patients aged 12 to 16 years, treated with hGH 20 IU/kg/yr from 1 to 6 years for isolated GH deficiency. LHRHa was injected IM monthly (3.7 mg in 2 patients, 1.8 in 2) from the onset of pubertal stage P2. The mean ± SD data before and after 12 months of LHRHa therapy were as follows : growth velocity (SDS) decreased from -1.79 ± 0.34 to -1.93 ± 0.46 for chronological age and increased from -0.80 ± 0.90 to -0.55 ± 1.11 for bone age ; plasma testosterone (ng/ml) decreased from 1.95 ± 0.77 to 0.10 ± 0.05 ; ratio of bone age to height age (BA/HA) decreased from 1.12 ± 0.12 to 1.05 ± 0.10.

Though preliminary, these results seem encouraging. Treatment with LHRHa allowed maintenance of plasma testosterone at pre-pubertal levels. Since control studies in pubertal patients with isolated GH deficiency treated with hGH alone showed an insufficient growth spurt, it is likely that the association of LHRHa with hGH may allow the improvement of final height.