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MODIFICATION OF 24 HOUR GROWTH HORMONE (GH) SECRETION AFTER CONTINUOUS SUBCUTANEOUS INJECTION (CSI) OF GRF (1-29) NH_2 DURING 3 WEEKS IN 6 CHILDREN WITH PARTIAL GH DEFICIENCY.

6 children (2 boys and 4 girls) with growth retardation (m = 2.8 ± 0.5 DS) were studied: mean chronological age was 11.9 ± 1.5 yr, mean bone age 9.3 ± 1.2 yr ; they were all Tanner stage I for pubertal development ; GH peak after 2 pharmacological tests were between 7 and 10 ng/ml, IC of GH was below 3 ng/ml/min. After an IV bolus of 1 ug/bw of GRF (1-29) NH_2, mean maximum GH peak was 30 ± 13 ng/ml ranging from 15 to 50 ng/ml. 24 hour GH secretion was studied before treatment and after one and 21 days of CSI of GRF. Travenol AS 6MP pumps were used, catheter and syringes were previously tested for GRF adhesion. The dose of GRF used was either 20 or 40 ug/bw/day. On day one, mean 24 hour IC of GH increased from 2.3 ± 0.4 to 5.7 ± 3.3 ng/ml/min, maximum GH peak from 13 ± 4 to 35 ± 20 ng/ml and the number of GH peaks above 5 ng/ml rose from 3.7 ± 0.8 to 6.8 ± 3.3. Among the 3 children (1 boy and 2 girls) receiving 20 ug/bw/day of GRF, only one increased his 24 hour IC of GH up to 3 ng/ml/min (from 2.31 to 4.74 ng/ml/min), but this result was obtained in the 3 children receiving 40 ug/bw/day. After 21 days of such treatment the mean value of 24 hour IC of GH was 5.2 ± 3.3 ng/ml/min, the mean maximum GH peak 28 ± 18 ng/ml and the mean number of GH peaks was 7.5 ± 2.9. In all but one child, the response to GRF (1-29) NH_2 decreased whatever the dose used but the 24 hour IC of GH remained above 3 ng/ml/min when this value was obtained on day one. Local and general tolerance was good.
In conclusion : the effect on 24 hour GH secretion after CSI of GRF (1-29) NH_2 depend on the dose, normalization of 24 hour IC of GH was obtained in all cases when the dose was 40 ug/bw/day, this effect decreased after 21 days.

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DOSE-RESPONSE STUDIES WITH BIOSYNTHETIC HUMAN GROWTH HORMONE IN GROWTH HORMONE DEFICIENT PATIENTS.

Increasing doses of biosynthetic human growth hormone (B-hGH) were given subcutaneously to 7 GH deficient subjects for three 14 days periods (2, 4 and 6 IU/day at 20.00 h) followed by 14 days without GH therapy. At the end of each period they were hospitalized for blood sampling. A dose-dependent increase in serum GH and somatomedin-C (Sm-C) levels occurred. However, the time course of the serum Sm-C patterns showed a significant fall in the evening during absence of therapy, a significant increase following injections of 2 IU of B-hGH, and constant levels within normal range during treatment with 4 and 6 IU. Plasma glucose was within normal range, with lower fasting levels (at 04.00 h) when no GH was given. Breakfast induced a plasma glucose rise when GH was administered, but no rise without GH, and a dose-dependent increase in the post-prandial insulin response. GH therapy increased serum levels of free fatty acids ($p < 0.05$) and 3-OH-butyrate but had no significant impact on serum triglyceride and cholesterol. We conclude that serum Sm-C levels show consistent GH dose-dependence, and that a GH replacement dose of 2 IU/day (1.5 IU/m^2/day) is insufficient to maintain normal diurnal levels. Furthermore, a GH independent diurnal variation in these patients is suggested, and finally it is demonstrated that this authentic GH preparation possesses diabetogenic and lipolytic actions.

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THE ABSORPTION KINETICS OF SUBCUTANEOUSLY ADMINISTERED GROWTH HORMONE: INFLUENCE OF INJECTION VOLUME.

Daily subcutaneous (sc) injections (inj) seems now to be the recommended mode of GH administration. A substantial sc degradation of exogenous GH has previously been reported. The aim of the present study was to evaluate the influence of inj volume on the sc absorption rate and bioavailability of GH. Fourteen healthy adults with a median age of 27.5 years and a normal body mass index participated. In a randomized design they all received 3 sc inj of 6 IU biosynthetic human GH (Norditropin^R) dissolved in either 0.5, 1.0 or 2 ml respectively. At least one week elapsed between each inj, which was given in the morning (8.00h) after which moderate physical activity was allowed. Blood was sampled hourly for 7 (n=14) to 12 (n=8) hours. The initial absorption rate (2 hour values) tended to be faster with the 2 ml inj volume (P=6.5%). The 2 ml inj volume also yielded the highest mean peak GH values: 23.7 ng/ml (2 ml), 14.7 ng/ml (1 ml) and 16.9 ng/ml (0.5 ml) (P<0.02), as well as the largest area under the curves (8-15 hours): 89.6 ngxhour/ml (2 ml), 62.7 ngxhour/ml (1 ml) and 67.8 ngxhour/ml (P<0.05). We therefore conclude that a large inj volume could imply a more rapid absorption as well as a larger bioavailability of sc injections GH. One could speculate that a rapid sc absorption diminishes the local degradation of GH and thus increases its bioavailability.

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PRESERVATION OF PHYSIOLOGIC SECRETION OF GROWTH HORMONE DURING TREATMENT OF IDIOPATHIC SHORT STATURE WITH GROWTH HORMONE (rhGH).

Twenty four hour secretory profiles of growth hormone were measured in 3 children with idiopathic short stature before and 48 hours after 6 months of treatment with rhGH. The study was undertaken to assess the possibility that exogenous GH might impair endogenous secretion. The children were all prepubertal (mean age 10.5yr±.8), with GH levels greater than 10 ng/ml on provocative testing. Growth velocity during therapy increased from a mean of 3.8±1.5 to 7.0±1.5cm/yr, ($p<0.001$). The repeat studies were carried out under identical conditions in the sleep laboratory. Total sleep time verified by sleep polysomnography and EEG recordings was identical in both studies (mean 503 vs 505 minutes). Comparison of pre and post treatment GH secretory profiles showed no attenuation of endogenous GH levels. Between pulses GH concentration was undectable in the pre and post rhGH treatment study.

	Serum GH conc. before rhGH mean (ng/ml)	GH peaks (n) conc.ofpool (ng/ml)		Serum GH conc. after rhGH mean (ng/ml)	GH peaks (n) conc.ofpool (ng/ml)	
Patient 1	2.2	2.6	7	2.0	1.8	6
Patient 2	0.9	0.8	2	1.3	1.0	3
Patient 3	3.1	2.3	6	5.6	5.3	5

We conclude that exogenous therapy does not interfere with maintenance of endogenous pulsatile secretion of GH. These data provide evidence for the resilience of the GH secretory system in the growing child.

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TREATMENT OF SHORT NORMAL PREPUBERTAL CHILDREN WITH GROWTH HORMONE.

The growth reponse to growth hormone (GH) was studied in 9 short normal prepubertal children (6 boys, 3 girls) with a low height velocity. Their average age was 8.2yr (range 4.7-12.1), height standard deviation score (SDS) for chronological age (CA) was -2.6 (-2.0 to -3.7). All had normal maximum plasma GH responses above 10ng/mL to stimulation with clonidine and/or insulin induced hypoglycemia. Assessment of overnight GH secretion by measurement of GH in 20min intervals for 12h yielded low peak levels of 8.7±3.0(SD)ng/mL and low mean pool values of 1.9±1.0. With informed consent treatment with somatrem (Protropin) 0.11±0.01mg/kg three times weekly s.c. was then begun and continued for one year. No major side effects were noted. After 6 months of GH therapy, height velocity SDS for CA increased significantly ($p<0.001$) from a pretreatment mean of -1.7 (-0.6 to -3.0) to +3.4 (-1.0 to +5.7), representing a change from 4.7cm/yr (3.5-6.0) to 9.3 (5.7-12.5). Height velocity during GH treatment (SDS for CA and cm/yr) inversely correlated with endogenous nocturnal peak GH concentration ($r=-0.76$, and $r=-0.78$; both $p<0.05$). We conclude that some short normal children with low height velocity and low endogenous GH secretion may profit from GH therapy. A major goal should be the proper identification of these patients and careful long-term follow-up to final height.
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PROSPECTIVE RANDOMISED STUDY OF LOW DOSE ETHINYL-OESTRADIOL AND OXANDROLONE IN TURNER SYNDROME (TS).

30 patients with TS, aged 4.6-12.6 years were randomly allocated to receive oral ethinyl oestradiol (EE2) (0.5-2.0ug/day) or oxandrolone (OX) (0.625-1.25mg/day). Groups were matched for age, karyotype, pre-treatment height SDS for TS and height velocity SDS for TS (HV SDS) (Ranke).

HV SDS results (SD) after 0.5-1.0 yrs were as follows:

	Pre-Treatment	Treatment	
EE2	0 (0.6)	+1.5 (1.3)	$p = 0.003$
OX	0 (0.7)	+2.4 (1.1)	$p < 0.002$

Response to EE2 was slightly less consistent than to OX ($p < 0.05$), with 2 non-responders.

Both treatments were well tolerated. Cliteromegaly was noted in 2 on OX; 3 on EE2 had early breast development.

24 hr growth hormone (GH) profiles were performed in 10 of each group before and during treatment. The sum of GH pulse amplitudes (SPA) was calculated using a computer algorithm (PULSAR). GH SPA was not changed by either treatment.

Used in appropriate dosage, both agents are safe, simple and effective agents in Turner syndrome. Neither appears to work via increased GH secretion.