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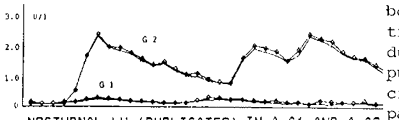
LH PATTERNS AT THE ONSET OF PUBERTY.

In advanced puberty a pulsatile LH pattern can be observed. In prepuberty absence of LH pulses may be real or due to insensitivity of the LH assay. LH patterns were studied in healthy boys(3 prepub.CA:11.3-14.3 yr,BA:11.0-11.5 yr,test.vol.(TV)<3 ml and 11 early pub. CA:11.5-13.4 yr, BA:11.0-12.5 yr, Tanner stage G2, TV ≥3 ml).Informed consent was obtained. Blood for LH estimation was sampled at 10' intervals from 12-18 hr and from 24-06 hr. A duoclonal IRMA, specific for LH with a sensitivity of 0.10 U/l (MAIAclone Serono) was used.
In the G1 boys LH was not detectable during daytime; at night during periods of 20-60' detectable but low (<0.5 U/l) values were observed. In the G2 boys most diurnal values were> 0.3 U/l with periods of values of 0.1-0.3 U/l; in 5 boys occasional pulses (<1.0 U/l were observed. At night definite pulses up to 3 U/l were observed in all boys; the median number of pulses was 4/6 hr.Conclusion: at the onset of puberty the still prepubertal boy has intermittant gonadotrophic activity only during the night; in early puberty this activity increases to a clear pulsatile pattern, sometimes with diurnal pulses as well.



NOCTURNAL LH (DUPLICATES) IN A G1 AND A G2

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THE METABOLIC CLEARANCE RATE, APPARENT DISTRIBUTION SPACE AND PLASMA HALF-LIFE OF UNLABELLED BIOSYNTHETIC HUMAN GROWTH HORMONE IN HYPOPITUITARY PATIENTS.

Previously published information on GH metabolism in GH-deficient patients is scarce and data are conflicting. We studied the metabolic clearance rate (MCR), plasma half-life ($T_{1/2}$) and apparent distribution space (DS) of unlabelled 'methionine free'-biosynthetic human growth hormone (B-hGH) using the constant infusion technique in seven hypopituitary patients, 6 males and 1 female, mean age 21 years (range 15-29 years). They received a constant intravenous infusion of B-hGH with a rate of 50 ng/kg/min for three hours. After stopping the infusion the disappearance of se-growth hormone was followed for another three hours. The MCR averaged 4.06 ml/kg/min ± 1.11 (SEM). $T_{1/2}$ was estimated by means of linear regression analysis, the mean value was 21.3 min ± 2.14 (SEM). The elimination was found to follow first order kinetics. The DS averaged 117.63 ml/kg ± 26.93 (±SEM). The present results demonstrate that the kinetics of B-hGH elimination is of first order and further that $T_{1/2}$ is of the same range as described in normal subjects.

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PHARMACOKINETICS AND SHORT TERM METABOLIC EFFECTS OF PITUITARY AND BIOSYNTHETIC HUMAN GROWTH HORMONE IN GH-DEFICIENT MAN. A DOUBLE-BLIND CROSSOVER STUDY.

In a double-blind crossover study we compared pituitary and 'methionine free' biosynthetic human growth hormone (P-hGH and B-hGH) with respect to pharmacokinetics and short term metabolic effects in 9 hypopituitary children.They treated themselves for 4 weeks with 2 IU subcutaneously (s.c.) daily at 20.00h. After admittance to hospital 2 IU was given intramusculary (i.m.) the first day, and s.c. the second.They then switched over to the alternative preparation.The pharmacokinetics of B- and P-hGH were identical. Comparing i.m. and s.c. absorption ,the latter was slower,and resulted in smaller areas under the curves,indicating greater local degradation.Both preparations caused identical increases in somatomedin C,but slightly more sustained after s.c. inj.P-glucose, -glukagon and s-insulin fluctuated within normal range.The glucose profile pointed at a modest anti-insulin effect of hGH when given in the morning.B-lactate,-alanine,-glycerol and -B-OH-butyrate,and s-TG,-cholesterol and -carbamide revealed no abnormalities with either hGH preparation.Finally,no development of anti-GH or E coli polypeptide antibodies was seen.In conclusion, the pharmacokinetics and short term metabolic effects of B-hGH and P-hGH were identical.Furthermore,the advantage of daily s.c. hGH injections in the evening is once more demonstrated.

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MONOMERIC SERUM CALCITONIN (M-CT) SECRETION DURING HUMAN GROWTH HORMONE (hGH) REPLACEMENT OF GH-DEFICIENT CHILDREN (GHD).

hGH administration to children with GHD is associated with increased bone turnover and tubular phosphate (P) reabsorption. Both mechanisms are important for enhenced somatic growth and may be regulated by other factors than GH or SM-C. We therefore studied the role of M-CT, the biological active form of calcitonin, as a possible mediator of hGH on P and bone metabolism. Ca stimulated (2mg/kg/5min iv) CT-M (ΔCT-M) was measured with a new silica extraction method before and during hGH replacement in 8 prepubertal children with GH in comparison to 16 controls (C) and 8 constitutional tall children (T). ΔM-CT (mean±SEM) was 36±10 in untreated GHD, 24±4 in C, and 14±4 pg/ml in T (GHD vs T, $P<0.05$). During **treatment** with 2U/m^2/d sc hGH, ΔM-CT decreased significantly in GHD to 16±4 pg/ml after 1 month, remaining suppressed during 12 months. hGH induced a parallel increase of growth rate, alkaline phosphatase, osteocalcin, urine hydroxyproline and tubular transport maximum for P (TmP/GFR), the latter being negatively related to ΔM-CT ($r=-0.47$, $n=32$, $P<0.01$) **Conclusion:** hGH suppresses M-CT secretion, explaining in part its increasing effect on bone turnover and renal phosphate conservation.

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TREATMENT WITH hGH HAS NO EFFECT ON ADULT HEIGHT IN HYPOPITUITARY CHILDREN

Adult height of hypopituitary children following treatment with human pituitary growth hormone (hGH) is disappointingly low despite the fact that hGH administration before puberty results in accelerated statural growth without unduly accelerating bone maturation. Our study showed that the range of adult heights was similar for various types of hypopituitary growth retardation; this range did not undergo an appreciable upward shift after hGH treatment. Evaluation of hGH effectiveness for a well-defined type, that of multiple pituitary hormone deficiency following breech birth, disclosed that adult height was not dependent on the presence of hGH (14 patients with hGH averaged 162.9 cm (SEM 1.93), 10 patients without hGH 159.5 cm (SEM 3.49)). However, adult heights were reached at earlier ages (with hGH at 22.3 y (SEM .38), without hGH at 25.7 y (SEM .54)). The duration of the pubertal spurt in growth brought about by androgen treatment was reduced by hGH from 9.5 y (SEM .91) to 5.5 y (SEM .45). Skeletal maturation must have been faster during androgen with hGH than during androgen alone. More detailed follow-up studies are needed, particularly in view of the imminent rise in the number of patients that will undergo treatment with biosynthetic growth hormone. Earlier treatment with higher or more frequent doses may be required to improve effectiveness of GH on adult stature.

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EVIDENCE OF LOCAL DEGRADATION OF SUBCUTANEOUSLY INJECTED BIOSYNTHETIC HUMAN GROWTH HORMONE IN HYPOPITUITARY PATIENTS.

In a previous study we observed that subcutaneously (s.c.) injected human growth hormone (hGH) resulted in significantly lower serum growth hormone profiles (AUC) than after intramuscular (i.m.) administration. In the present study we compared the steady state serum concentrations of continuous infused biosynthetic human growth hormone (B-hGH) via the s.c. and i.v. route in 7 hypopituitary subjects, 6 males and 1 female, mean age 21 years (15-29). The rate of B-hGH infusion was 50 ng/kg/-min. I.v. infusion was performed for 3 hours, giving a mean steady state concentration of 17.3 ng/ml ± 3.3 (SEM). Following a three hours intermission the s.c. infusion was commenced lasting 19 hours and resulted in significantly lower serum concentration, 5.0 ng/ml ± 1.0 (SEM) ($p < 0.001$). In four of the subjects the s.c. infusion was extended for a further 24 h with a steady state mean serum concentration of 6 ng/ml ($p > 0.2$). These findings strongly suggest a local subcutaneous degradation of injected hGH in these subjects. The exact mechanisms cannot be deduced from our results but must await further investigation.