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The induction of puberty by low dose pulsatile GnRH

Eight patients (3 F, 5 M) have been treated with low dose pulsatile GnRH to induce puberty using two different dose regimens. In 7 the hypogonadotrophic hypogonadism was idiopathic and in one followed surgery and radiotherapy for a posterior fossa astrocytoma. Mean age at commencement of treatment was 16.3 years (14.3 to 19.7).

One girl and one boy were treated continuously throughout 24 hr with GnRH 15 µg subcutaneously every 90 mins. Ovarian changes were detected by ultrasound after one week and a 'multicystic' appearance after 8 weeks. Breast development to Stage 2 was seen at 4 months but failed to progress due to 'down regulation'. Plasma testosterone in the boy increased from <1 to 23 nmol/L in 9 months when the genetalia were Stage 5 and a growth spurt had occured.

Six patients have been treated with nocturnal pulsatile GnRH 2 µg subcutaneously every 90 minutes for 6 months. Two girls had a detectable ovarian ultrasound response in one week and a progression in pubertal staging by 3 months. Four boys have shown a diurnal variation in plasma testosterone from evening values <1 nmol/L to morning values >4 nmol/L. Testicular enlargement occured before 3 months of therapy. All patients have been monitored by serial nocturnal plasma profiles of gonadotrophins, prolactin, growth hormone and testosterone or oestradiol.

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Pubertal growth in patients with testicular feminisation(Tfm).

Spontaneous pubertal growth was studied in 8 patients with classic Tfm, and the effect of exogenous estrogens in 1(gonadectomized (GE) before puberty). Mean chronologic age (CA) at peak height velocity(PHV) was 12.7yrs,which is closer to CA at PHV in normal girls(NG,12.4) than in normal boys (NB,13.9). Mean PHV(7.4 cm/yr) was as in NG(7.3 cm/yr)),but significantly lower than in NB(9.3).Conjugated estrogens in the GE-patient started at CA 10.2yrs caused a PHV of 12cm/yr. Bone age(BA) corresponded better to NB than to NG standards. Adult height is 172.3±4.1cm(n=6,2 not yet adult).It is significantly lower than in NB(-0.6±0.7SD),but higher than in NG (+1.4±0.8 SD). Adult height in the GE-patient is only 160.5cm. Body proportions(n=3) are as in NG (sitting height (SH)+0.8, subischial leg height(SILH)+ 0.6SD).Compared to NB, the legs are relatively short (SH-0.4,SILH-0.9SD).Tfm-patients provide a model to study estrogen effects without interference of androgens.It is concluded that in NG the pubertal growth spurt also is mostly due to the action of estrogens rather than of adrenal androgens, and that physiological estrogen replacement in hypogonadism should not be started late,but at the appropriate BA in order to ensure normal pubertal growth.

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Pharmacodynamics of [DesGly^{10},D-Ser(t-Bu)]^{6}-GnRH EA in 6 normal volunteers and in 2 girls with precocious puberty

The behaviour of [DesGly^{10}, D-Ser(t-Bu)]^{6}]-GnRH EA (HOE 766) has been studied in plasma and urine after intranasal (IN,200 ug) or subcutaneous (SC,10 ug/kg) administrations . A RIA for HOE 766 and its metabolites has been developed using ^{125}I-[DesGly^{10}, DTrp^{6}]-GnRH EA (Gift of Dr. J. Rivier) as tracer and an antiserum to HOE 766 (gift of Dr. H. Fraser). Crossreaction with native GnRH was only 1.7 %. Sensitivity was 1 pg/tube. In 6 male adolescents, mean plasma HOE 766 concentration (±SE) was 0.46±0.08 , 0.50±0.10, 0.28±0.04, 0.24±0.04, 0.13±0.03, and 0.08 ±0.02 ng/ml, 30, 60, 90, 120 and 180 min. after IN administration. Urine excretion of HOE 766 metabolites was 9.4±2.0 ug/4h. There was a good correlation between plasma and urine levels (r=0.92). In the same 6 volunteers, plasma HOE 766 levels were 21.2±3.0, 25.9±0.8, 21.2 ±0.9, 17.1±0.7, 12.8±1.1, 8.9±0.4, and 5.9±0.8, 20, 40, 60, 120, 180 and 240 min. after the SC injection. In two girls with precocious puberty followed during 3 months with IN treatment, urine excretion of HOE 766 was in good correlation with the degree of inhibition of E_2 and of LH and FSH responses to GnRH. The monitoring of HOE 766 metabolites in the urine thus appears to be helpful for the evaluation of the intranasal therapy of precocious puberty with GnRH analog.

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Results of treatment with an LHRH agonist (HOE 766) in true precocious puberty (P.P.)

The efficiency of D-SER(TBU)6-LHRH 1-9 EA10(Buserelin,HOE 766) was assessed in 6 children (5 girls,1 boy) with P.P. [idiopathic (2),hypothalamic hamartoma(2),arachnoid cyst(1),hydrocephaly(1)]. Age at beginning of treatment, was 4 10/12 to 8 5/12 yr with advanced bone age between 3 1/12 and 6 2/12 yr ; all girls had menstruated. The boy was successfully treated by intranasal route (200 µg t.i.d.) with serum T falling (3.6 to 0.2 ng/ml) and testicular volume regression. The 5 girls receive 20 µg/kg/d sc and results at 6 mo therapy are shown below (mean±sem) ; in 4 girls seen at 9 mo E_2 was maintained below 20 pg/ml;1 girl with hydrocephaly was poorly controlled. The growth rate (n=6) calculated over 9 mo decreased from 9.1 ± 0.6 to 6.6 ± 0.6*** cm/y.

	Peak FSH(mui/ml)	Peak LH (mui/ml)	E_2 (pg/ml)	VM index
PreRx	14.63±2.72	62.4 ± 17.68	47 ± 12	51 ± 1.7
3 mo	4.84 ±0.46***	9.9 ± 1.96**	21 ± 0.9	23 ± 12*
6 mo	4.2 ±0.64***	5.56 ± 1.33***	8.46 ± 2.79**	16 ± 8**

LRF test (100µg/m² IV)-Paired t test by comparison with PreRx p*<0.05, **0.02, ***0.01-VM index : vaginal maturation index.

In conclusion, HOE 766 suppresses gonadal steroid secretion and is an effective therapy in children with P.P. However since this pilot study, 2 children were resistant to 20 µg/kg/d sc and were controlled with higher dosage (30 µg/kg/d) indicating individual sensitivity to this analog.

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The B domain of Insulin-like Growth Factor I (IGF-I) is recognized by IGF carrier proteins but not by type II IGF receptors.

IGF-I and IGF-II are highly homologous to each other and to proinsulin. Although the IGFs and insulin have similar biological activities and receptor reactivity, IGF carrier proteins and one subtype of IGF receptors (Type II) interact exclusively with the IGFs and not with insulin. To determine the structural basis for this specificity, we have prepared 3 synthetic hybrid molecules that combine different portions of the IGF and insulin molecules: A27(Ins)-B(Ins), in which the A chain of insulin is extended by the D domain of IGF-II; A(Ins)-B(IGF-I) and A27(Ins)-B(IGF-I)in which the B domain of IGF-I is combined with the natural or extended A chain of insulin. In a competitive binding assay with acid stripped carrier protein from adult rat serum, ^{125}I-rIGF-II binding was inhibited by the IGFs and by both hybrid molecules containing B-(IGF-I), but not by insulin or A27(Ins)-B(Ins). Qualitatively similar results were obtained with carrier proteins from human serum, neonatal rat serum and rat liver cell conditioned media. By contrast, none of the three hybrids molecules inhibited ^{125}I-rIGF-II binding to Type II IGF receptors on rat liver, placenta or chondrosarcoma cells. CONCLUSIONS: The B domain of IGF-I but not the D domain of IGF-II allow Insulin-IGF hybrid molecules to be recognized by IGF carrier proteins. Neither domain is involved in binding to Type II IGF receptors.

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Pulsatile administration of GRF 1-44 to male patients with Growth-hormone-deficiency and normal men.

We investigated the possibility of inducing a physiological GH pattern by exogenous administration of GRF 1-44 in a pulsatile manner in order to modify the condition resulting from a hypothalamic defect. Three adolescent patients with short stature and four normal men responded to a pulsatile i.v.-administration of GRF 1-44 with a clear increase in the GH levels. No patient was on GH therapy at the time of the study. After a 12 hour nocturnal plasma profile of GH, cortisol, PRL and glucose (blood samples every 20 min) all subjects received 50 µg GRF 1-44 i.v. at 8 and 10 a.m. and every second hour for 12 hours during the following night. Blood samples were taken every 20min to evaluate pituitary response. Results: Patient 1 did not show any spontaneous nocturnal GH pulses but responded to pulsatile GRF stimulation with GH levels of 1.5 to 6.7 ng/ml in the morning and from 3.0 to 15.8 ng/ml at night, thus proving hypothalamic GRF deficiency. Patients 2 and 3 both had 4-5 spontaneous nocturnal GH peaks ranging from 8-40 ng/ml. GH responses to pulsatile GRF were between 10.4 and 109 ng/ml at morning and between 12.3 and 114 ng/ml during the night. The characteristic circadian plasma profiles of cortisol, PRL and glucose remained intact. In the volunteers, spontaneous nocturnal GH peaks ranged from 5.8-17.5 ng/ml, whereas GH responses to pulsatile GRF peaked at 9.1-54 ng/ml in the morning and at 20-73 ng/ml during the night. Conclusions: Our preliminary results suggest (1) that pituitary sensitivity to exogenous pulsatile GRF is markedly higher during the night than in the morning and (2) that a normal circadian GH pattern can be induced in GRF deficient patients by pulsatile GRF.