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LINEAR GROWTH AND SKELETAL MATURATION IN CHILDREN WITH PRECOCIOUS PUBERTY (PP) TREATED BY A LONG-ACTING PREPARATION OF DTrp 6 LHRH (Trp 6).

50 children with PP, 37 girls aged (mean ± SD) 6.6 ± 2.2 and 13 boys aged 7.6 ± 3.1 years, were treated for 30 months with monthly muscular injections (60 µg/kg) of DTrp 6, which normalized plasma gonadotropin and sex steroid levels. Before treatment mean height and bone ages were respectively 8.0 ± 2.6 and 9.1 ± 2.5 years in girls (HA/BA = 0.88 ± 0.1), 8.4 ± 3.1 and 8.9 ± 3.2 in boys (HA/BA = 0.93 ± 0.1). Height velocities (HV) were 10.8 ± 3.6 cm in girls, 11.0 ± 3.5 cm in boys. During the first 6 months HV and skeletal maturation remained accelerated and the HA/BA ratio decreased : 0.87 ± 0.1 in girls, 0.91 ± 0.09 in boys. After 6 months, HV decreased significantly to 5.5 ± 2.0 cm/year in girls ($p < 0.001$) and 5.7 ± 1.6 in boys ($p < 0.005$) while skeletal maturation decreased abruptly leading to a progressive and significant increase of HA/BA ratio reaching at 30 months 0.97 ± 0.08 in girls ($p < 0.001$) and 1.04 ± 0.08 in boys ($p < 0.025$). Mean growth hormone peak after ornithine was 13.6 ± 1.4 ng/ml before Trp 6, 12.3 ± 2.6 ng/ml after (NS) in both sexes and no correlation was found between plasma somatomedin C levels and HV. This data indicates that, in children of both sexes with PP, the perfect control of gonadotropin and gonadal secretions obtained by DTrp 6 leads, after a short delay, to a significant improvement of height prognosis.

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FRENCH COLLABORATIVE STUDY ON EFFECT OF 3 YEARS LHRH ANALOGUE (LHRHa) TREATMENT ON GROWTH AND BONE MATURATION IN CENTRAL PRECOCIOUS PUBERTY (CPP).

The LHRHa have been shown to suppress the secretion of gonadotropins and sex steroids in children with CPP and therefore to improve their predicted final height. The present study was designed to evaluate the course of growth, BA and predicted height after prolonged and complete suppression of gonadal activity. 50 children (42 girls, 8 boys) with CPP were fully controlled by Buserelin (HOECHST), 20-30 ug/kg/d sc, for a period up to 3 yr. At onset of therapy, their mean CA was 7.1 ±0.3 yr with BA-CA > 2 yr, VMI > 35, E2 > 25 pg/ml in girls, T > 1 ng/ml in boys and normal GH-AITT secretion. After 1 mo mean peak plasma LH and FSH after LHRH decreased respectively from 17.4 ±3 to 3.6 ±0.5 mU/ml (***) and from 10 ± 1 to 2.4 ± 0.2 mu/ml (***). After 3 mo plasma E2 in girls and T in boys decreased respectively from 38.3 ±2.6 to 18 ±2 pg/ml (***) and from 4 ±0.6 to 0.5 ±0.3 ng/ml (**). Thereafter no significant change of these parameters was observed over 3 yr.

Duration of treatment (n)	-1yr	0 (50)	+1yr (50)	+2yr (14)	+3yr (4)
Growth rate (cm/yr)	9±0.4 ***	7.6±0.4 ***	5±0.8	4.6±1.3	
Bone age (yr)		10.2±0.3**	11.2±0.3	12±0.3	12.5±0.1
Predicted height (SD)		-1.8±0.2*	-1.5±0.2	-1.3±0.2	-0.2±0.3

m ± sem *p < 0.05, **p < 0.01, ***p < 0.001

In conclusion: 1) after 3mo, LHRHa Buserelin given sc 20-30 ug/kg/d induced a decrease of gonadal sex steroids to prepubertal levels which persisted over 3 yr. 2) the relatively greater slowing of skeletal maturation, in comparison to growth rate, produced an increase in predicted final height by 1.6SD over 3 yr. The comparison between predicted final height at the beginning of the LHRHa treatment and final height will allow us to evaluate the real effect of this therapy.

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EFFECTS OF THE SLOW-RELEASE GNRH AGONIST DECAPEPTYL-DEPOT (DD) IN CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY (CPP): PITUITARY-GONADAL FUNCTION, CLINICAL COURSE AND PHARMAKOKINETICS OF DECAPEPTYL.

In an international multicentre trial of (DD) for treatment of CPP, a total of 76 patients, 68 girls and 8 boys, are presently enrolled. There are 50 (3 boys) naive patients (group I) and 26 (5 boys) who have been treated with either cyproterone acetate or Buserelin before (group II). Basal plasma LH (mIU/ml) decreased from 3.3 ± 0.3 (mean ± SE) and 2.8 ± 0.5 to 2.4 ± 0.3 and 1.6 ± 0.3 after 1 year of therapy in groups I and II, resp.. The LH response to GnRH i.v. was signif. ($p < 0.001$) reduced in both groups from 45.1 ± 3.8 and 30 ± 6.4 mIU/ml to 4.2 ± 0.9 and 2.9 ± 0.9 mIU/ml. Similar results were obtained for FSH. Spontaneous nocturnal LH secretion was pulsatile before agonist therapy and prepubertally low after 3 or 6 months. At the same time, E_2 levels fell signif. from 118 ± 12 to 52 ± 4 pmol/l ($p < 0.01$) in group and from 93 ± 22 to 36 ± 5 pmol/l in group II. Clinical signs of gonadarche showed either regression or complete arrest. Decapeptyl plasma levels determined by RIA after extraction showed a highly variable course after i.m. injection of DD, reaching maximum levels between 30 and 120 min. 4 weeks after the last injection, DD plasma levels ranged from below sensitivity (30 pg/ml) to 567 pg/ml. There seemed to be no correlation between 4-week Decapeptyl levels and plasma E_2. Except of short injection pain (anaesthetic spray helpful), no side effects were seen. We conclude that treatment of CPP with DD, given only every 4 weeks i.m., leads to an effective suppression of the pituitary-gonadal axis without clinical escapes, despite variable and sometimes very low plasma levels of the drug.

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PLASMA Sm-C AND GROWTH RETURN TO NORMAL VALUES IN CHILDREN TREATED BY LHRH ANALOGUE FOR TRUE PRECOCIOUS PUBERTY.

During central precocious puberty (CPP) elevated plasma Sm-C/IGF I levels have been observed, with a significant decrease during short term suppression by LHRH analogues (LHRHa). The present study was designed to evaluate the course of Sm-C after a prolonged and complete suppression of gonadal activity. 16 children (13 girls and 3 boys) with idiopathic (n=11) or organic (n= 5) CPP were fully controlled by Buserelin, 20-30 µg/kg/d sc for a period up to 3 years. At onset of therapy their mean CA was 6 4/12 ± 6/12 yr with a mean BA advance of 3 10/12 ± 6/12 yr and gonadal activity with vaginal maturation index (VMI) >35, E2 >25 pg/ml in girls, T >1 ng/ml in boys and normal GH secretion. The Sm-C values from time of full control (VMI <35 or T < 0.5 ng/ml) are as follows, by comparison to growth rates (m ± sem)

Duration of control (n)	before (16)	6mo (13)	12mo (13)	18mo (4)	24mo (3)	36mo (2)
growth rate (cm/yr)	10.2±0.5	7.2±0.7	6.5±0.5	3.6±0.6	4.5±0.6	4.7
Sm-C (u/ml)	2.7±0.5	2.6±1.0	1.8±0.3	1.5±0.3	1.1±0.1	0.8

Sm-C values reached normal for CA prepubertal values only 24-36 mo after full suppression of gonadal activity. This was correlated with growth changes ($p < 0.05$)

In conclusion 1) these data show that a long time is necessary before full return to normal for CA of plasma Sm-C, 2) a positive correlation between Sm-C and growth favours the role of GH and Sm-C in the pubertal growth spurt, 3) the return of Sm-C to normal values for CA is an additional indication of control by LHRHa therapy.

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PUBERTAL MATURATION OF THE GONADOTROPIN α-SUBUNIT (Gnα) RESPONSE TO LH-RH IN NORMAL AND PATHOLOGICAL CONDITIONS.

Gnα is secreted in synchronism with LH pulses and is responsive to LH-RH administration. The changes of the Gnα response to LH-RH test were investigated throughout puberty in boys and girls. Gnα was measured by RIA, the assay specificity being assessed by chromatography on Sephadex G100. Basal and peak responses to LH-RH (x̄±sem, ng/ml) were respectively, in prepubertal boys (n=4) = 0.54± 0.22 and 3.4± 0.19, in pubertal boys (stage 2-3, n=4) : 0.88 ± 0.21 and 5.68 ± 0.71, in prepubertal girls (n=4) : 0.30 ±0.15 and 4.30 ±1.67, in pubertal girls (stage 2-3, n=4) = 0.44 ± 0.29 and 6.50 ± 1.96, in follicular phase (n=4) 1.40 ± 0.39 and 7.40 ± 1.18. Peak values were significantly higher in pubertal than in prepubertal subjects. In 13 girls with precocious puberty basal and peak values were respectively 0.77 ± 0.21 and 12.1 ± 1.5 before treatment, 2.6 ± 0.85 and 7.86 ± 1.19 after 6 months of therapy with D-TRP-6-LH-RH (Decapeptyl microcapsules). In adolescents with hypopituitarism (n=4), Gnα peak after LH-RH was only 0.28 ± 0.18, in contrast with the high response in Klinefelter syndrome (n=4, 10,18 ± 2,71) and in Turner syndrome (n=4, 32.7 ± 6.33). This study confirm the parallelism of Gnα and LH secretions in various situations except in subject treated with a LH-RH agonist.

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GONADAL CONTROL OF PULSATILE SECRETION OF LH AND FSH IN PREPUBERTAL BOYS

LH and FSH secretion was examined in 6 normal boys and 6 boys with primary hypogonadism (HG) by measuring plasma levels at 15 min intervals for 6 h during day and night with a supersensitive (0.019 IU/l and 0.014 IU/l) time-resolved immunofluorometric assays. In each group 5 boys were at stage P1 and 1 at P2. At stage P1 the mean concentration of LH was significantly higher at night than during day in 3 of the 5 boys in each group, FSH levels were higher only in 1 normal boy and 1 with HG. LH and FSH pulses were detected in all boys. Of the LH and FSH pulses 62% occured at night and had higher amplitudes than daytime pulses. Forty percent of the pulses consisted of both LH and FSH. Mean FSH levels and pulse amplitudes were higher ($p<0.001$) in HG than in normal boys. (Table)

	Mean conc.(IU/l)		Pulses/12h		Pulse amplitude (IU/l)	
	controls	HG	controls	HG	controls	HG
LH	0.50	0.41	4	3.25	0.34	0.78
FSH	0.84	3.15	4	3.25	0.18	1.05

At stage P2 the mean concentrations, pulse amplitudes and frequencies of LH and FSH were higher than at P1, and the boy with HG had 10 times higher levels than the normal boy. Our results show, that even in prepuberty the gonads appear to control the gonadotrophin secretion, which is pulsatile already before puberty.