

DECREASE IN GROWTH HORMONE (GH) AND SOMATOMEDIN C (SOMC) DURING LHRH AGONIST (LHRHa) TREATMENT OF CENTRAL PRECOCIOUS PUBERTY (CPP), Craig R. Rudlin, M. Joan Mansfield, John F. Crigler, Jr, Karin A. Karol, John D. Crawford, Paul A. Boepple, William F. Crowley, Jr, Harvard Medical School, Departments of Pediatrics, Medicine and Gynecology, Boston, MA, USA

LHRHa suppresses both gonadotropin pulsations and sex steroids and slows height velocity (HV) in patients with CPP. To evaluate GH's role in this slowing of growth, sleep induced GH secretion (20 min. samples, 10 PM-2 AM) and SOMC (10 PM) were measured in 9 pre-adrenarchal girls with CPP (ages at onset 1.6-6.3 yrs, M=3.8; bone ages advanced a mean of 3.7 years). Therapy suppressed gonadotropin pulsations, response to LHRH, estradiol and maturation indices in all patients. Growth velocity fell from  $14.4 \pm 1.7$  cm/yr (Mean  $\pm$  SEM, all measurements) pretherapy to  $8.7 \pm 1.4$  after 6 mos of therapy ( $p=0.0005$ ). SOMC levels decreased from  $3.1 \pm 0.7$  IU/ml pretherapy to  $1.3 \pm 0.2$  at 3 mos ( $p=0.009$ ) and  $1.4 \pm 0.2$  at 6 mos ( $p=0.007$ ). Nocturnal peak levels fell from  $25.4 \pm 6.8$  ng/ml pretreatment to  $9.1 \pm 1.7$  at 3 mos ( $p < 0.01$ ) and  $7.5 \pm 1.1$  at 6 mos of therapy ( $p < 0.01$ ). Total GH secreted during the 4 hr interval decreased a mean of 58% at 3 mos and 48% at 6 mos compared to pretreatment. The accelerated HV in CPP patients under 6 years is associated with increased GH and SOMC production. With LHRHa induced suppression of gonadal steroids, both HV and GH and SOMC production are decreased.

D-SER(TBU)<sup>6</sup>EA<sup>9</sup>LHRH IN PRECOCIOUS PUBERTY: PHARMACOKINETICS OF SC, IV AND INTRANASAL USE.

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The LHRH analog, D-Ser(TBU)<sup>6</sup>EA<sup>9</sup>LHRH(LHRHa) effectively controls the clinical and endocrinological progress of central precocious puberty in both sexes, when provided once daily by SC injection, or by intra-nasal (IN) spray given 8 hourly (J. Clin. End. & Metab. 1984: 58,966). To define the pharmacokinetics of LHRHa in this condition, we developed a RIA, utilizing an antibody generated against a hemocyanin conjugate of LHRHa, in which there is no crossreactivity with natural LHRH, LH or FSH. Recovery by RIA of added LHRHa in normal human serum or urine, ranged from 93 to 105%. During treatment with SC injection, 30  $\mu$ g/kg, peak levels of LHRHa of  $42.1 \pm 7.4$  ng/ml (mean  $\pm$  SEM) occurred at 30 min, with  $t_{1/2}$  of 71.4 min (n,5). Only 21% of given dose was excreted in urine at +3 h. With the IN route, 5.3  $\mu$ g/kg (200  $\mu$ g fixed dose) peak levels were seen at 30 min (n,7) but were 1000 fold lower in concentration ( $0.34 \pm 0.13$  ng/ml). Only 0.6% of the dose was excreted at +3 h. After IV injected 10  $\mu$ g/kg in 3 adult volunteers, peak levels of >3500 ng/ml occurred at 1-2 min,  $t_{1/2}$  was 38.2 min and 17.4% was recovered in urine at 3 h. These data indicate: (1)  $t_{1/2}$  and elimination rate of this LHRHa is significantly greater than natural LHRH; (2) low dose LHRH at frequent intervals probably provides optimal treatment; (3) urinary LHRHa by specific RIA can be used as a guide to patient compliance.

INTRANASAL LHRH ANALOGUE TREATMENT OF IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY IN GIRLS. Tsu-Hui Lin, Mary E. LePage, Milan Henzl, John L. Kirkland.

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Daily administration of LHRH analogues (agonists) has been documented to decrease biochemical findings and clinical signs of true precocious puberty. We have treated 10 girls, age 14 months to 9 years, with true idiopathic precocious puberty by intranasal inhalation of Nafarelin Acetate ([D-Nal(2)6]LHRH), 800-1500  $\mu$ g/day for 4 to 11 months. 9 girls showed decelerated growth velocity (from  $9.7 \pm .8$  to  $5.8 \pm .8$  cm/yr.  $p < 0.005$ , paired t test, n=8). 4 of these 9 girls were menstruating prior to therapy and all girls stopped menses subsequent to therapy. These 9 girls' estradiol levels also decreased significantly (from  $46.3 \pm 12.3$  to  $9.3 \pm 1.8$  pg/ml,  $p < 0.01$ , paired t test) as well as their 24 hour urinary LH levels (from  $7.5 \pm 1.8$  to  $2.7 \pm 0.5$  iu/day,  $p < 0.01$ , paired t test). The girl who did not respond to nasal inhalation therapy was administered subcutaneous injections of the same LHRH analogue. All children received intranasal inhalation without any observed side effects. These results suggest that most girls with true precocious puberty can be treated with intranasal administration of Nafarelin Acetate, a new LHRH analogue. (Supported in part by USPH Grant RR-00188 from the General Clinical Research Centers Branch, National Institutes of Health).

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PARADOXICAL RISE OF GROWTH HORMONE AFTER ORAL GLUCOSE LOAD IN TALL GIRLS: A PHYSIOLOGICAL FINDING IN PUBERTY?

In 153 healthy tall girls (age  $13.2 \pm 1.5$  SD, bone age  $12.7 \pm 0.9$  SD), oral glucose tolerance tests (50 mg/m<sup>2</sup>) were carried out, before treatment with high dose steroid hormones, for the exclusion of risk factors. Besides glucose and insulin, plasma growth hormone (GH) was measured in order to see whether increased GH concentrations could be related to growth data. 141 girls had a height > 2 SDS (T), 12 girls with a height < 2 SDS served as controls (C). GH (mU/l) was analyzed during 0-60' and 120-240' after oral glucose. GH results: A paradoxical rise (>10) during 0-60' was seen in 41.5% T and in 25% C; an exaggerated response (>65) during 120-240' occurred in 23% T and in 40% C. "Normal" GH results, i.e. low or suppressed values (<10) during 0-60' were seen in 58.5% T and 75% C; moderate peaks (25-65) during 120-240' occurred in 54.9% T and 50% C; no increase was found in 22.1% T and 10% C. The differences in frequency during 0-60' and 120-240' between T and C are statistically not significant. Girls with a paradoxical rise vs. suppressed values 0-60', and girls with exaggerated vs. "normal" response 120-240' did not show any difference with respect to height, weight, height prediction, target height, puberty, etc. The large number of girls with non-suppressible and/or exaggerated GH secretion as well as the lack of any correlation between GH values and clinical data suggest, that this "inappropriate" GH-secretion may be a physiological phenomenon in puberty.

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EFFECTS OF ETHINYLESTRADIOL AND TESTOSTERONE OENANTHATE ON PITUITARY GONADOTROPINS, GONADAL STEROIDS AND SEX HORMONE BINDING GLOBULIN IN PUBERTAL BOYS AND GIRLS TREATED FOR TALL STATURE.

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16 girls and boys were treated for tall stature. Their height prediction was above 185 cm and 205 cm, respectively. The girls received 0.5 mg of ethinylestradiol (EE<sub>2</sub>) daily. The mean plasma level of EE<sub>2</sub> was  $596 \pm 82$  (SE) ng/ml. The gonadotropins were suppressed from pubertal values (LH  $1.8 \pm 1.0$ ; FSH  $1.8 \pm 1.9$ ) to low infantile or not measurable levels (LH  $0.6$  to  $< 0.3$ ; FSH  $0.9$  to  $< 0.3$   $\mu$ g/l). Estradiol (E<sub>2</sub>) was also suppressed to infantile values ( $29 \pm 13$  pg/ml) while testosterone (T) remained unchanged ( $294 \pm 38$  pg/ml). The sex hormone binding globulin (SHBG) increased 4-fold from pubertal values ( $7.7 \pm 1.3$   $\mu$ g/ml) to high levels as usually seen in late pregnancy ( $31.3 \pm 6.4$   $\mu$ g/ml). The boys were treated with 500 mg of testosterone oenanthate (TO) i.m. every 2 weeks. The mean plasma level of T was 10218 pg/ml ranging from 1760 pg/ml at day 13 to peak levels of 22380 pg/ml at day 4. The gonadotropins were suppressed to low infantile values or below the detection limit (LH  $0.3$   $\mu$ g/l; FSH  $0.4$  to  $0.3$   $\mu$ g/l). The E<sub>2</sub> levels remained within the normal male pubertal range ( $36 \pm 12$  pg/ml). The SHBG in these patients decreased by 57% to  $1.8 \pm 0.2$   $\mu$ g/ml below the normal male range ( $3.1 \pm 0.3$   $\mu$ g/ml). The mean T/SHBG ratio increased 5-fold from 1018 to 5676. - Androgen action in boys is best reflected by the T/SHBG ratio. SHBG indicates estrogen action in girls. It's measurement may help prevent overtreatment in estrogen replacement therapy in hypogonadal girls.

EFFECT OF ETHINYLESTRADIOL ON MELATONIN AND ON OVULATORY CYCLES IN TALL GIRLS.

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Department of Pediatrics, University of Hamburg, Germany, FRG. Girls suffering from tall stature (height prediction >185 cm) were treated with 0.5 mg ethinylestradiol (EE<sub>2</sub>) which led to a mean plasma level of  $596 \pm 82$  (SE) pg EE<sub>2</sub>/ml. Plasma melatonin of 23 girls determined in hourly intervals before, during, and after therapy showed normal day-night fluctuations as compared with a control group of 5 healthy adolescents. During therapy (n=12) the night peak values at 3 a.m. were lower ( $70 \pm 6$  pg/ml) than prior to ( $92 \pm 13$ ) and following ( $83 \pm 9$ ) therapy. These findings indicate a slight melatonin suppressing effect of EE<sub>2</sub>. 27.7  $\pm$  17 (SD) months following cessation of therapy the ovaries of 15 girls (17.9  $\pm$  5 yrs. of age) were monitored by endocrine and sonographic studies at day 9, 15, and 20 of the menstrual cycle. Peak values of estradiol ( $165 \pm 47$  pg/ml) and of LH/FSH ( $2.0 \pm 0.8/2.3 \pm 0.8$   $\mu$ g/l) were found at day 15 in 13 out of 15 girls. Follicular diameter estimated by ultrasound was  $11.8 \pm 3.5$  mm at day 8, enlarged up to  $19.1 \pm 3.2$  mm at day 15, and had disappeared at day 20, when progesterone was elevated ( $3.6 \pm 1.3$  ng/ml). There was no endocrine and no sonographic evidence for an ovulation in 2 patients only. Our data suggest high incidence of ovulatory cycles following EE<sub>2</sub>-treatment comparable with data found in non treated normal girls 5 years after menarche<sup>1</sup>.

1. Metcalf, M.G. et al.: J Endocrinol 97(1983)213

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