177 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 ± 1.7 cm/yr (Mean ± SEM, all measurements) pretherapy to 8.7 ± 1.4 after 6 mos of therapy ($p=0.0005$). SOMC levels decreased from 3.1 ± 0.7 IU/ml pretherapy to 1.3 ± 0.2 at 3 mos ($p=0.009$) and 1.4 ± 0.2 at 6 mos ($p=0.007$). Nocturnal peak levels fell from 25.4 ± 6.8 ng/ml pretreatment to 9.1 ± 1.7 at 3 mos ($p<0.01$) and 7.5 ± 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.

178 D-SER(TBU)^{6}EA^{9}LHRH IN PRECOCIOUS PUBERTY:PHARMACOKINETICS OF SC, IV AND INTRANASAL USE. F.John Holland,Leona Fishman,D.Colm Costigan, J.Steven Leeder, Atilla T.Fazekas,Univ of Toronto; Hosp for Sick Children, Toronto; Hoechst Pharm Inc, Montreal, Canada.

The LHRH analog,D-Ser(TBU)^{6}EA^{9}LHRH(LHRH$_a$) 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 LHRH$_a$ in this condition, we developed a RIA,utilizing an antibody generated against a hemocyanin conjugate of LHRH$_a$, in which there is no crossreactivity with natural LHRH, LH or FSH. Recovery by RIA of added LHRH$_a$ in normal human serum or urine, ranged from 93 to 105%. During treatment with SC injection,30 µg /kg, peak levels of LHRH$_a$ of 42.1 ± 7.4 ng/ml (mean ± SEM) occurred at 30 min, with $t_{½}$ of 71.4 min (n,5). Only 21% of given dose was excreted in urine at +3 h. With the IN route, 5.3 µg/kg (200 µg fixed dose) peak levels were seen at 30 min (n,7) but were 1000 fold lower in concentration (0.34 ± 0.13 ng/ml). Only 0.6% of the dose was excreted at +3 h. After IV injected 10 µg/kg in 3 adult volunteers, peak levels of >3500 ng/ml occurred at 1-2 min, $t_{½\beta}$ was 38.2 min and 17.4% was recovered in urine at 3 h. These data indicate:(1) $t_{½}$ and elimination rate of this LHRH$_a$ is significantly greater than natural LHRH; (2) low dose LHRH at frequent intervals probably provides optimal treatment; (3) urinary LHRH$_a$ by specific RIA can be used as a guide to patient compliance.

179 INTRANASAL LHRH ANALOGUE TREATMENT OF IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY IN GIRLS. Tsu-Hui Lin, Mary E. LePage, Milan Henzl, John L. Kirkland. Baylor College of Medicine, Department of Pediatrics, Houston, Texas and Syntex Laboratories, Department of Clinical Medicine, Palo Alto, CA.

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 µ g/day for 4 to 11 months. 9 girls showed decelerated growth velocity (from 9.7 ± .8 to 5.8 ± .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 ± 12.3 to 9.3 ± 1.8 pg/ml, $p<0.01$, paired t test) as well as their 24 hour urinary LH levels (from 7.5 ± 1.8 to 2.7 ± 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).

180 Urs Eiholzer, Toni Torresani, Hans Bucher, Andrea Prader, Ruth Illig, University of Zurich, Department of Pediatrics, Zurich, Switzerland.

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 ±1.5 SD, bone age 12.7 ±0.9 SD), oral glucose tolerance tests (50 mg/m^2) 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' occured 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' occured 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.

Supported by the Swiss National Science Foundation Grant No. 3.906.0.83

181 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_2)daily. The mean plasma level of EE_2 was 596± 82(SE)ng/ml. The gonadotropins were suppressed from pubertal values (LH 1.8±1.0;FSH 1.8±1.9)to low infantile or not measurable levels (LH 0.6 to< 0.3;FSH 0.9 to< 0.3 µg/l). Estradiol(E_2)was also suppressed to infantile values(29± 13 pg/ml)while testosterone(T)remained unchanged (294±38 pg/ml). The sex hormone binding globulin(SHBG)increased 4-fold from pubertal values (7.7±1.3 µg/ml) to high levels as usually seen in late pregnancy (31.3±6.4 µg/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 µg/l;FSH 0.4 to 0.3 µg/l).The E_2 levels remained within the normal male pubertal range (36±12 pg/ml). The SHBG in these patients decreased by 57% to 1.8±0.2 µg/ml below the normal male range (3.1±0.3 µg/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.

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

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Girls suffering from tall stature (height prediction >185 cm) were treated with o.5 mg ethinylestradiol (EE_2) which led to a mean plasma level of 596 ± 82 (SE) pg EE_2/ml. Plasma melatonin of 23 girls determined in hourly intervalls 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 (7o ± 6 pg/ml) than prior to (92 ± 13) and following (83 ± 9) therapy. These findings indicate a slight melatonin suppressing effect of EE_2. 27.7 ± 17 (SD) months following cessation of therapy the ovaries of 15 girls (17.9±5 yrs. of age) were monitored by endocrine and sonographic studies at day 9, 15, and 2o of the menstrual cycle. Peak values of estradiol (165 ± 47 pg/ml) and of LH/FSH (2.o ± o.8/2.3 ± 8 ug/l) were found at day 15 in 13 out of 15 girls. Follicular diameter estimated by ultrasound was 11.8 ± 3.5 mm at day 8, enlarged up to 19.1 ± 3.2 mm at day 15, and had disappeared at day 2o, when progesterone was elevated (3.6 ± 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_2-treatment comparable with data found in non treated normal girls 5 years after menarche [1].

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

This study was supported by DFG (Co 119/1-1)