

ONTOGENESIS OF HEPATIC EPIDERMAL GROWTH FACTOR (EGF) METABOLISM IN NORMAL BALB MICE. Nilsa P. Laborde, Gertrudis G. Buenaflor, Pam L. Brown, Martin S. Grodin, Carlos C. Callegari, Delbert A. Fisher, UCLA School of Medicine, Harbor-UCLA Medical Center, Department of Pediatrics, Torrance, CA.

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To characterize the ontogenesis of the hepatic EGF system in normal Balb mice, we measured serum and liver concentrations of EGF, and liver concentrations of pre-pro EGF mRNA and EGF receptor binding. Male and female animals were studied at 1,2,3,5,7 and 10 wks of life. After sacrifice, body weight and length were measured and serum and liver tissues were collected for EGF determinations. Immunoreactive serum EGF (mean ± SEM) increased at 7 and 10 wks and was significantly higher (p<0.05) in males (465±53 and 683±120 pg/ml) than females (188±52 and 235±64 pg/ml). Liver EGF concentrations were low at 1,2,3 and 5 wks, significantly increasing (p<0.01) at 10 wks to 268±50 and 179±36 pg/μg protein for males and females (males versus females p<0.05 at 10 wks). EGF receptor binding of ¹²⁵I-EGF was low at 1,2 and 3 wks increasing to 5.03±0.83 and 5.79±1.02 (fm/μg membrane protein) in males and 1.84±0.64 and 2.36±0.28 in females at 5 and 10 wks respectively. Values were significantly lower (p<0.01) in females. Pre-pro EGF mRNA was examined at 1,2,3,5,7 and 10 wks. EGF message increased in liver to highest values at 10 wks in both males and females. Conclusions: There is a parallel increase of serum and liver EGF concentrations, and liver EGF mRNA between 5 and 10 wks of postnatal life. EGF receptor binding also increases during this time. The results suggest that newborn liver may be an important source of circulating EGF in Balb mice.

PHARMACOKINETICS OF T₃ AND T₄ AFTER ACUTE THYROXINE OVERDOSE: EFFECT OF PTU AND IOPANOIC ACID. Peter G. Lacouture, William J. Lewander, Enrique Silva, Frederick H. Lovejoy, Harvard Medical School, Children's Hospital, Dept. of Medicine, Boston, MA.

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Over a 1 yr period, 15 ingestions of thyroxine in children under 5 yrs of age were evaluated. All patients had initial serum T₄ levels determined within 7 hrs of ingestion. Multiple T₃ and T₄ serum levels were determined in 7 patients. Peak T₄ levels ranged from 16-118 mcg/dl with 3 patients >75 mcg/dl. The estimated peak T₄ level occurred <12 hrs in 71% of the patients; the estimated peak T₃ level occurred >20 hrs in 71% of the patients. In 5 patients who received no specific treatment, the mean serum T₄ t_{1/2} was 2.84 da (range 1.7-4.54 da) and the mean serum T₃ t_{1/2} was 5.1 da (range 1.9-12.3 da). Specific therapy to inhibit conversion of T₄ to T₃ was given in 2 patients during which serum t_{1/2} were:

	mean T ₄ t _{1/2}	mean T ₃ t _{1/2}
Before Treatment	2.2 da	3.6 da
During Treatment	20 da	1.6 da

We conclude that in acute pediatric overdose of thyroxine: (1) peak T₄ levels occur earlier than peak T₃ levels, (2) in untreated patients the t_{1/2} of T₄ is shorter than T₃, and (3) shortly after administration, PTU and iopanoic acid can prolong T₄ t_{1/2} and shorten T₃ t_{1/2}.

BONE DENSITOMETRY IN CONGENITAL ADRENAL HYPERPLASIA (CAH). Mary M. Lee, Frances Ackland, Stephen Dahlem, Sidney Heyman, Thomas Moshang, Jr., Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Department of Pediatrics & Radiology, Philadelphia, PA

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Glucocorticoid therapy in CAH is titrated to maintain adequate adrenal suppression while avoiding the consequences of steroid excess. Although adrenal steroid levels may acutely reflect overdosage, chronic overtreatment is often suspected only after growth failure and retardation of bone age are noted. Osteoporosis is a known complication of steroid therapy and has been described in CAH. Photon absorptiometry is a simple, precise and noninvasive method of measuring bone demineralization. It may afford a more sensitive measure of steroid overtreatment than a bone age film, with less radiation exposure. We measured bone density in 20 CAH patients (10 males and 10 females) using the linear radiation model SP-2 bone mineral analyzer and correlated the findings with steroid levels as well as clinical aspects related to glucocorticoid treatment.

Preliminary data show that there is some correlation between bone density and glucocorticoid management of CAH. All the patients with elevated or borderline elevated adrenal steroid levels had bone density values in the normal range. 3 of 5 girls with biochemical values suggesting overdosage had bone density values in the range consistent with demineralization. None of these 3 had any decline in growth velocity and bone ages done in 2 of the 3 showed no delay. These preliminary data suggest that bone densitometry may be of benefit in monitoring therapy in CAH patients and may result in the earlier detection of oversuppression.

DEMONSTRATION OF DISRUPTED GONADOTROPIN FEEDBACK IN GONADAL FAILURE DURING CHILDHOOD BY LHRH ANALOGUE. Peter A. Lee, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Department of Pediatrics, Pittsburgh, PA 15213.

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The use of LHRH analogues as antagonists is well studied. Use of intermittent LHRH analogue (Lupron) as an agonist in the diagnosis or treatment of gonadal disorders is being investigated. To validate its effect, 4ug/kg/2X week SQ injections were given to 8 males with delayed puberty. After one month, urinary LH and FSH levels (ug/24h) were significantly greater the day after injection than the day before (LH 41.8 ± 6.5 vs 22.8 ± 7.4, p < 0.003, FSH 63.5 ± 9.0 vs 40.9 ± 11.9, p < 0.011).

During childhood, inappropriate gonadotropin secretion may not be apparent and the diagnosis of gonadal failure may not be possible. The use of intermittent LHRH analogue as an agonist in six prepubertal male children, aged 5-12y, resulted in a rise of LH and FSH over 6 weeks. Values in 5 normal patients:

wk	Testosterone			LH (ng/ml)			FSH (ng/ml)		
	0	3	6	0	3	6	0	3	6
M	23.0	94.7	36.0	<4.9	13.1	39.4	43.5	55.5	77.0
SE	7.2	61.4	18.3	-	4.1	24.5	10.1	5.3	10.1

Pt #6: 4yr. old with non-palpable testes

10 23 32 6.0 101.7 171.7 769.2 1026.5 1434.1
LHRH analogue stimulation resulted in an abnormal rise of LH and FSH without significant testosterone response. This demonstrates an abnormal feedback mechanism in childhood. This procedure may be a useful diagnostic test for evidence of gonadal failure in children.

GROWTH HORMONE DEFICIENCY IN CHILDREN WITH PRECOCIOUS PUBERTY: TREATMENT WITH AN LHRH ANALOGUE. Tsu-Hui Lin and John L. Kirkland, Baylor College of Medicine, Department of Pediatrics, Houston, TX.

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Sex steroid hormones can accelerate linear growth in children with growth hormone (GH) deficiency (GHD) without GH therapy. Therefore, GHD may not be suspected in children who are in puberty. LHRH analogue (LHRHa) therapy in children with precocious puberty (PP) has been demonstrated to decelerate the rapid growth velocity associated with elevated sex steroid hormones. We report two children below with PP in whom GHD was diagnosed after their linear growth was decelerated by intranasal administration of LHRHa (Nafarelin).

Patient	CA	BA	GRa	GRb	GRc
1	8.75	12.75	7.2	1.5	5.0
2	5.5	9.5	8.4	2.5	10.2

CA=chronological age in years; BA=bone age in years; GR=growth rate in cm/year: a=before LHRHa therapy, b=during LHRHa therapy, c=combined LHRHa and GH therapy

GHD in children with PP may be more common than suspected previously. Recognition of this fact is important since a major complication of PP is short stature as an adult. The combination of GH and LHRHa therapy provided a more normal growth velocity for these children. These findings suggest that for some children with GHD, LHRHa therapy may be indicated to optimize their final adult height. (Supported by FD-R-000097 and USPH RR-00188)

EFFECTS OF GROWTH HORMONE ON BONE DENSITY IN CHILDREN WITH TURNER SYNDROME. Tsu-Hui Lin, Rebecca T. Kirkland, Adrian D. LeBlanc, Harlan Evans and John L. Kirkland, Baylor College of Medicine, Department of Pediatrics and Nuclear Medicine, Houston, TX.

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Children with Turner syndrome (TS) frequently have asymptomatic osteoporosis by radiologic diagnosis. Growth hormone (GH) has been considered as a therapeutic or preventive measure for osteoporosis. GH also has been demonstrated to be effective in improving growth velocity in children with TS. This study was designed to determine the changes in bone density associated with GH therapy.

Eight children with TS (45,X in 3; 45,X/46,Xq in 1; 45,X/46,X, idic(X) in 1; 45,X/46,X, idic(Y) in 1; 45,X/46,X,rX(p11q22); and 45,X/46,X, iso(Xq) in 1) were studied between chronological ages of 7 to 13 with bone ages of 3 to 11 years. The bone density changes were assessed by dual beam photon densitometry with a program modified for children. The area studied was L2-L4. Bone density was measured every 6 months. Each patient served as her own control for 6 months before GH therapy was started. GH was administered intramuscularly three times weekly at a dosage of 0.125 mg/Kg/dose. Changes in bone density at 6 months of control period was 0.020±1.975 gm/cm²/yr (mean±SEM). During six months of GH therapy changes in bone density was 0.007±0.021 gm/cm²/yr (P > 0.05). This indicates a lack of effectiveness of GH therapy on bone density in children with TS. Further study is required to determine if this lack of effectiveness is because the children were growing or because children with TS may respond differently from the general population.