

#### 402 AGE-RELATED VASCULAR EFFECTS OF PROSTAGLANDIN D<sub>2</sub> (PGD<sub>2</sub>). K.A. Welch, R.K. Lyrene, A. Dew, J.E. Phillips (Spon. by G. Cassidy). Univ. of Alabama in Birmingham, Dept. of Peds., Bham, AL.

PGD<sub>2</sub> infusions decrease mean pulmonary arterial pressure (Ppa) and resistance (PVR) in both fetal and hypoxic, neonatal lambs, yet cause direct pulmonary constriction in hypoxic juveniles. We gave bolus PGD<sub>2</sub> to 19 acutely-operated lambs, 4-24 days old(d). Normoxic lambs were given 1 and 10 µg/kg with recovery time between doses. The lambs were then ventilated with 13% O<sub>2</sub> and given the same doses of PGD<sub>2</sub>. We compared % Δ of Ppa, mean systemic arterial pressure (P<sub>as</sub>), and PVR in lambs <7d and ≥14d.

<7d				≥14d			
N	1µg	H	N	10µg	H	N	10µg
%ΔPpa	9±20	-26±10#	56±31#	-27±14#	36±26#	-12±15	60±18#
%ΔPVR	15±32	-28±13#	97±70	-38±11#	59±57#	-14±16#	60±15#
%ΔP <sub>as</sub>	25±8#	23±10#	42±6#	24±12#	22±12#	11±8#	15±12#

x ± SD; N = normoxia, H = hypoxia; #p < 0.05 from zero change.

In normoxic lambs, 1 µg/kg had no effect on Ppa and PVR at <7d but caused significant increases in ≥14d animals. Ten µg/kg raised Ppa and PVR in both younger and older normoxic lambs. In hypoxic animals, both doses lowered Ppa and PVR in the <7d group, while in the ≥14d lambs there was little or no pulmonary effect. P<sub>as</sub> was significantly increased by PGD<sub>2</sub> in all groups at both doses. We conclude that the pulmonary vasodilator effect of PGD<sub>2</sub> in hypoxic neonatal lambs decreases with advancing postnatal age, and that by 14 days, PGD<sub>2</sub> is no longer an effective pulmonary vasodilator.

#### 403 PHARMACOLOGY OF PANTETHINE IN NEPHROPATHIC CYSTINOSIS Carl T. Wittwer, Jess G. Thoene University of Michigan School of Medicine, Department of Pediatrics, Ann Arbor, Michigan

Oral D-pantethine (PI) as a source of cysteamine in the treatment of nephropathic cystinosis was investigated in two cystinotic patients who were treated with 70-1000 mg/kg/day PI. WBC cystine, and plasma and urinary pantothenate (PA) were measured by RIA. Only PA (no PI) was found in the plasma and urine of PI-treated patients. After a single 30 mg/kg dose, plasma PA levels at 0, 1/4, 1/2, 1, 2, 4, 8, and 24 hours were consistent with an open two compartment model with rate constants of ca. 0.04/hr for elimination and >1.0/hr for distribution. Peak plasma PA (10 nmol/ml) occurred at 2 hr, and the apparent volume of distribution was 77 liters for a 49 kg boy. Near linearity with dose was found for plasma PA (r=0.97, slight concavity upward) and PA excretion (r=0.97, slight concavity downward). Average PA excretion from the slope of the linear regression line was only 5% of the dose. At 1000 mg/kg/day, plasma PA was 180 nmol/ml, 300 times baseline. Increased stool frequency (3-4/day) was the only significant side effect. Plasma cholesterol decreased from 251 to 204 mg/dl over an 18 day course of 1000 mg/kg/day PI, supporting this agent's role as a hypolipidemic. 50-60% WBC cystine depletion was achieved. Although PI is apparently passively absorbed and hydrolyzed to PA and cysteamine in the intestine and/or plasma, limited absorption producing only modest WBC cystine depletion suggests this agent may not be useful in the treatment of cystinosis.

#### 404 INFANTS OF MOTHERS TREATED WITH LITHIUM (Li) DURING PREGNANCY HAVE AN INCREASED INCIDENCE OF PREMATURITY, MACROSOMIA AND PERINATAL MORTALITY. M.C. Yoder, J. Belik, R.A. Lannon, G.R. Pereira. (Spon. by W.W. Fox). Dept. of Peds., Univ. of PA Sch. Med., & Children's Hosp. of Phila., PA; Univ. Calif at S.F., Langley Porter Psych. Inst., San Francisco, CA.

We have previously described the association between maternal Li therapy during pregnancy and fetal macrosomia (Ped Res 17(4):304A, 1983). This study reviews the records of 241 infants reported to the Register of Lithium Babies between 1962-1978. All infants were included in calculating mortality statistics. Gestational age (GA), birthweight (BW), sex, Li dose and duration of therapy were analyzed in 180 infants. Premature delivery occurred in 39% of the pregnancies. Mothers of premature infants were treated with higher daily Li doses during the 1st and 2nd trimester than mothers of term infants (1.2 ± .6 gm vs. .9 ± .5 gm (1st trim.), p < .001 and 1.0 ± .8 gm vs. .8 ± .5 gm (2nd trim.), p = .06). Macrosomia (BW > 90th %tile for GA) was identified in 36% of the infants with a higher frequency in infants born prematurely than in those born at term (59% vs. 26%). The degree of macrosomia was significantly more pronounced in premature infants than in full term infants (129 ± 23 vs. 106 ± 18, % mean BW for GA, p < .0001). Perinatal mortality was 8.3% (projected 83 deaths/1000 live births) and included 8 stillbirths. Premature delivery accounted for 42% of the perinatal deaths. This study demonstrates that maternal use of Li (particularly greater than 1 gram daily in the 1st and 2nd trimester) during pregnancy constitutes a significant risk of premature delivery and fetal macrosomia. Prenatal management of these high risk pregnancies should include close monitoring for excessive intrauterine growth and premature labor.

#### 405 THE EFFECT OF MATERNAL RITODRINE(R) TREATMENT UPON RAT PUPS ADRENAL CATECHOLAMINE(CA) CONTENT. W.P. Zeller, J. Hannigan, C. Menendez, K. Ozog, A. Shanahan, C. Anderson, and R.M. Hurley. (Spon. by Lewis E. Gibson) (Supp R&E#050-12-211) Loyola University, Stritch School of Medicine, Foster G. McGaw Hosp. Department of Pediatrics, Maywood, IL 60153.

The tocolytic agent R is used to prevent premature labor by direct effects (β-agonist) upon uterine smooth muscle. The pharmacology of R is much like the CA epinephrine(EPI) in its metabolic effects. Since R is EPI-like, the effects on pup adrenal CA content was investigated by delivering to the Dam pharmacologic R (13.8 mg/M<sup>2</sup>/hr), by subcutaneous osmotic mini-pump on days 15-27 gestation. Control Dams were identical to R treated except pups contained saline. On day 21 pups were taken by C-section and adrenals were immediately processed for CA analysis by high performance liquid chromatography with electrochemical detection. The EPI was significantly reduced (+28%) in the R treated group; no effects were seen in dopamine(DA) or norepinephrine(NE) content.

R (n = 27)	DA (ng/gland)	NE	EPI
	17.1 ± 3.1	16.6 ± 1.8	70.4 ± 4.4*
Saline(n=18)	15.1 ± 4.6	16.4 ± 2.2	97.9 ± 12.6

The decreased adrenal EPI content is most likely due to either displacement of EPI by R and/or an inhibition of EPI synthesis. The mechanism and ramifications of R's effect on pup adrenal EPI content remain to be established.

## ENDOCRINOLOGY

#### 406 ACQUIRED HYPOPIUITARISM AFTER REYE'S SYNDROME, Indu Agarwal, Michael J. Bourgeois, Surendra K. Varma, Texas Tech University Health Sciences Center, Department of Pediatrics, Lubbock, Texas.

Growth failure after Reye's Syndrome was studied in a 14 year old white male. He had Reye's Syndrome at age ten years and also had loss of vision, which later improved considerably in the right eye. After recovery from Reye's Syndrome, he had no increase in linear growth during the following four years. From 75th percentile, his height dropped to below 5th percentile. His sexual maturation was in Tanner Stage I and funduscopic examination revealed optic atrophy on the left side with right disc being normal. He was admitted for complete neuroendocrine work-up at this time which showed a low Somatomedin-C level, subnormal growth hormone response to arginine-glucagon stimulation test (maximum growth hormone level of 1.2 ng/ml), subnormal TSH response to TRH stimulation (maximum TSH level of 5 mIU/ml) and a normal metyrapone test. Serum LH and FSH were 7 and <1 mIU/ml respectively. Urinary sp.gr. and osmolality were within normal limits indicating normal posterior pituitary functions. CT scan of the head showed small old infarct in right occipital lobe with slightly prominent CSF space. The bone age was compatible with his height age. Subsequently, patient has been started on Human Growth Hormone and levo-thyroxine treatment and response has been satisfactory. These results indicate hypopituitarism and optic atrophy following Reye's Syndrome. These complications after Reye's Syndrome have not been reported before. The patients with Reye's Syndrome should be monitored for subsequent growth failure and visual complications.

#### 407 GROWTH HORMONE (hGH) THERAPY AND TUMOR RECURRENCE OF CHILDREN WITH BRAIN NEOPLASMS AND HYPOPIUITARISM.

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We report on 34 children (17 males, 17 females) with brain tumors, including craniopharyngiomas (18), germinomas (4), astrocytomas (3), chromophobe adenomas (3), medulloblastomas (2), glioma (1), dermoid (1), retinoblastoma (1), and metastatic rhabdomyosarcoma from the pelvis (1). At the initiation of tumor therapy, which consisted of surgery with and without radiotherapy, mean age was 9.3 yrs. (0.4-17.8 yrs). Post tumor therapy, 94% of the patients were GH deficient. 24/34 patients received hGH. Annual growth rate before and after 1 yr. of hGH was 1.9±0.7 cm/yr and 5.6±2.8 cm/yr, respectively. 11 patients had 12 recurrences. 8 of 24 receiving hGH had recurrence of tumor within 0.5-36 mos.; 16 were tumor-free 8-72 mos. after initial therapy. Patients with tumor recurrence had a markedly lower annual growth rate during the first year of hGH than those without recurrence (mean 3.5±1.3 cm/yr vs 6.2±2.5 cm/yr, p<0.01). 3/11 patients with recurrence had not received hGH therapy; however, 1 was receiving IM testosterone monthly.

In conclusion, 24 of 34 patients with brain tumors and hypopituitarism received hGH therapy. 8/24 (33%) had tumor recurrence, compared to 3/10 (30%) who did not receive hGH, and 1/10 who was receiving testosterone. The data suggest that hGH therapy is not associated with increased rate of tumor recurrence.