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PHARMACOLOGY OF INTRAVENOUS VITAMIN E IN THE VERY LOW BIRTHWEIGHT (VLBW) NEWBORN. Paul R. Myers, The Children's Hospital Denver, Barbara J. Quissell, University of Colorado Health Sciences Center, Robert G. Peterson, Children's Hospital East Ontario, Dept. of Pediatrics.

Vitamin E (VE) has been used via the oral or in route in VLBW infants; however, the intravenous route is often preferred. The pharmacokinetics of intravenous VE have not been reported.

Prior to an infant study, we measured VE pharmacokinetics in 8 adult cats after an intravenous infusion. Results showed a mean $T_{1/2}$ of 73.0 hours, volume of distribution based on area (VD) of 0.59 l/kg and total plasma clearance (PC) of 4.5 mg/k/hr.

We then measured serum VE levels in six VLBW newborns after a one-hour infusion of 10 mg/kg (dl-α-tocopherol, Hoffman-LaRoche) via peripheral vein. Serum was obtained at 0, 0.5, 2, 6, 12, 24, 48, 72, 96 and 120 hours and then intermittently up to 28 days post infusion. Serum VE levels were measured by HPLC. Kinetic analysis was done using a multicompartment fitting with an exact, least squares program on a digital computer. All infants were n.p.o. and intubated for respiratory distress. Their mean BW was 920 grams and G.A. was 27 weeks. Select serum VE levels in mg/l:

Time (hrs)	0	0.5	24	180
Mean (range)	6(4-8)	88(66-106)	28(19-44)	18(14-23)

The mean $T_{1/2}$ was 282 ± 164 hrs., VD was 0.373 ± 0.098 l/kg, and PC was 1.27 ± .46 ml/k/hr. There was no change in liver function as assessed by clinical course, SGOT or bilirubin. Serum lipid concentrations were stable. Dosing recommendations can be based on these data.

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PLASMA BETA ENDORPHIN CONCENTRATION IN NEONATES WITH ACUTE STRESS. Ulla Neilsen, Koravangattu Sankaran, K. Wayne Hindmarsh and Valerie G. Watson, Perinatal Research Laboratory, Department of Pediatrics and College of Pharmacy, University of Saskatchewan, Saskatoon.

Plasma beta endorphin concentrations (β-ED) were measured in two groups of neonates with and without stress. The control group (Group 1) consisted of 20 infants with a mean ± SE gestational age and birthweight of 31.5 ± 0.60 weeks and 1720 ± 137.39 g respectively. Blood samples were collected at a mean postnatal age of 1 ± 0.3 days. Group 2 consisted of 23 infants with evidence of acute illness and significant stress who had a mean ± SE gestational age of 33.2 ± 1.1 weeks and a mean birthweight of 2075 ± 225 g. Their blood samples were collected at a mean postnatal age of 3.41 ± 1.30 days. β-ED was isolated in a manner previously described by the authors (Hindmarsh) utilizing Sephadex G-50 column chromatography and subsequent radioimmunoassay. The mean β-ED concentration in Group 1 was 27.8 ± 2.6 pg/ml and 63.9 ± 4.2 pg/ml in Group 2 ($p<0.05$). No correlation was observed with gestation or birthweight and β-ED concentration in Group 1, however, in Group 2, a positive correlation was seen with gestational age and plasma β-ED concentration ($r = 0.4411$) suggesting an increased production of β-ED with increasing gestation when faced with significant stress. In conclusion, neonates release endorphin in response to acute stress.

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GLYCOGEN PHOSPHORYLASE (GP) STIMULATION BY VASOPRESSIN (V), ANGIOTENSIN II (A2), GLUCAGON (GLU) AND A23187 IN NEWBORN HEPATOCYTES A. Noguchi, P. Jett, (Spons. by Wm. J. Keenan), Dept. of Pediatrics, St. Louis University.

Glycogenolysis is regulated by cAMP dependent and independent mechanisms in adult rat liver. Ontogeny of cAMP independent process is unclear. V and A2 stimulate GP by Ca dependent-cAMP independent mechanism as opposed to cAMP dependent GLU. A23187 bypassing surface receptors, alters cytosolic Ca(Ca signal) and stimulates glycogenolysis mimicking hormone action. Rat hepatocytes were in vivo isolated postnatally to examine GP activation by hormones in control and PTU treated (17 d gestation on) hypothyroid rats. GP was expressed hormone/basal; (M±SE%). n=6-8 each.

		5d	15d	28d	Adult
CONTROL	V	116±9	154±16	167±10*	172±13
	A2	126±8	154±19	162±13*	167±13
	Glu	205±7	196±14	213±16	193±12
	A23187	162±11	187±20	228±16§	200±12§
PTU	V	128±12	131±22	131±9	------
	A2	129±15	140±15	120±12	------
	Glu	250±32	199±26	223±8	------
	A23187	166±21	189±20	204±18	------

*:>PTU $P<0.03$, §:>5d $p<0.05$. T_4 replacement restored V and A2 responses of PTU by 28 d. Thus in newborn hepatocytes 1)V and A2 not GLU responses are weaker and modulated by thyroid hormone 2)A23187 response is lower. We speculate 1)V and A2 receptors as well as site distal to Ca signal are involved in the maturation of cAMP independent glycogenolytic process and 2) cAMP independent glycogenolysis is less active in newborn period.

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DOSE FORMULATION AFFECTS ORAL BIOAVAILABILITY OF ISONIAZID (INH). Daniel A. Notterman, Michael A. Nardi and Judy G. Saslow. (Spon. by R.G. Schacht). New York University Medical Center, Department of Pediatrics, New York.

Children too young to ingest an intact tablet of INH are frequently given untested formulations of the drug, since the commercial liquid syrup (P-I-N Forte, Lannett: INH 50 mg & pyridoxine HCL 2.5 mg in 5 ml) (SYR) is neither widely available nor frequently mentioned in pediatric literature. INH has been orally administered after mixing crushed tablets with foodstuffs, or placing the parenteral dosage form (a clear solution) in a vehicle of fruit juice. The oral bioavailability of these formulations has not been previously studied. We examined 4 children (5-20 months) with tuberculosis. Each received 10 mg/kg test doses of different INH preparations on successive days: 1)IM injection(IM,N=4); 2)Oral syrup(SYR, N=3); 3)Crushed tablet mixed with applesauce(TAB,N=4); 4)parenteral solution in applejuice(SOL,N=3). The serum concentration of INH was determined at several intervals after the test doses. For each formulation, the range and means (x) of peak concentrations (ug/ml) were: 1)IM 5.8-11.4 x=7.7; 2)SYR 5.6-8.3, x=6.9; 3)TAB 0.9-3.7, x=2.1; 4)SOL 2.5-3.3, x=3.0. After TAB, peak concentration occurred later (about 2 hours) than after SYR (1 hour or less). The mean area under time-concentration curve (AUC) was lower after TAB (12 ug/ml· hrs) than after IM (21 ug/ml· hrs), indicating limited absorption of this preparation.

Peak levels achieved after administration of TAB were lower and more variable than after administration of SYR or as reported by others after ingestion of intact tablets. Administering a crushed tablet of INH in applesauce does not reliably produce therapeutic serum concentrations of INH in children.

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ABSENCE OF TRANSSYNAPTIC BETA ADRENERGIC RECEPTOR REGULATION IN OVINE FETAL LUNG AND HEART. J.F. Padbury, D.H. Polk, R.W. Lam and A.H. Klein, UCLA School of Medicine, Harbor-UCLA Medical Center, Dept. of Pediatrics, Torrance, CA

We examined the effect of altered transsynaptic neural activity on lung and heart BAR development in the ovine fetus following chemical sympathectomy (CS) with guanethidine sulfate (GS). CS was induced by chronic administration of GS using subcutaneously implanted miniosmotic infusion pumps programmed to deliver 17 mg/kg/day for 14 days (4 animals). Control fetuses were infused with vehicle alone (4 animals). Animals were delivered by cesarean section. The extent of sympathetic denervation was assessed by measurement of tissue norepinephrine (NE) content using a sensitive, specific radioenzymatic assay. BAR concentration and affinity were measured using the tritiated radioligand dihydroalprenolol (DHA). Lung NE was unchanged following CS while cardiac atrial NE was 10% of control ($p<.001$) and ventricular NE was 19% of control values ($p<.001$). Lung and ventricular BAR were 112 and 100% of control values, respectively ($p>0.05$). Brown adipose tissue NE and adrenal catecholamine (CAT) concentrations were unchanged by CS. Conclusions: 1) GS at the dosage utilized causes extensive atrial and ventricular sympathetic denervation but does not affect lung, BAT or adrenal CAT contents. 2) Sympathetic denervation of the developing ventricle is not associated with up-regulation of BAR. Speculation: Myocardial BAR development in fetal life is not subject to the "normal" postpartum transsynaptic regulatory influences.

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VITAMIN E (VE) KINETICS IN INFANTS <1500 GRAMS: INTRAMUSCULAR (IM) VS. ORAL ADMINISTRATION

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Early VE use has been advocated to lessen severity of Retinopathy of Prematurity. Prematures are known to have cord blood VE levels lower than adult norms, but the ability of available VE preparations to raise these levels has not been studied. From 7/82 to 7/83, 30 infants (1500g were randomized into three groups. Group 1 (G-1) received a sesame oil preparation of dl-alpha tocopherol acetate (E-Ferol, O'Neal) as follows: a loading dose of 50 mg/kg IM within the first 12 hours of life and a maintenance dose of 20 mg/kg IM on days 2 through 7. Group 2 (G-2) received the same IM loading dose but maintenance doses of oral d-alpha tocopherol (Aquasol E, USV) at 25 mg/kg/dose every six hours by nasogastric tube on days 2 through 7. Osmolality was reduced to 557 mOsm/L by diluting 1:4 with sterile water. Group 3 (G-3) received only the oral drug at the above dose from day 1 through 7. Levels were measured in cord blood and 1, 3 and 7 days after VE was begun. Analysis was by high performance liquid chromatography with levels reported as mg/dl.

	N	BW(gm)	cord bld	1da.	3da.	7da.	
G-1	10	1165±215*	0.45±0.2	0.45±0.22	0.6±0.21	0.92±0.18	p<0.01
G-2	10	1099±285	0.43±0.1	0.63±0.37	1.7±1.14	2.7±1.7	
G-3	10	1081±276	0.36±0.1	0.78±0.26	1.52±0.53	2.33±1.06	

* S.D.

Three patients developed mild necrotizing enterocolitis (NEC) and were evenly distributed among the groups. The patient with NEC in G-1 had a VE level of 1.2 mg/dl on day 7. Those in G-2 and G-3 had levels above 4 mg/dl on day 7. Another patient from G-2 with a level of 6.8 mg/dl did not develop NEC. We conclude that oral Aquasol-E is more effective than recommended doses of IM E-Ferol in raising serum VE levels by age one week.