† 318 RISK FACTORS IN NEONATAL ADVERSE DRUG REACTIONS. Jacob V. Aranda, Patrick Seliske, Linda Horton, Judi Collinge, Eugene W. Outerbridge. Dev Pharmacol and Perinatal Research Unit, McGill Univ-Montreal Children's Hospital Research Institute, Montreal, Canada.

Factors associated with occurrence of adverse drug reactions (ADR - abnormal event(s) validated to be due to drugs) were evaluated in an intensive prospective epidemiologic study of 1200 neonates consecutively admitted to a neonatal intensive care unit. An MD/nurse team recorded and computerized all pertinent biographic, clinical, laboratory and medication data. 326/1200 (27.1%) neonates developed at least one ADR; 153 of whom had moderate to severe (fatal or life-threatening) ADR. Comparison of patients with ADR and those without ADR showed that ADR patients had significantly lower birthweights and gestational age with longer duration of hospitalization. Neonates <28 weeks gestation have 9-fold risk of ADR. Conversely, for term infants(>37 wks) the ADR relative risk was 0.5 . Diseases of prematurity (resp. distress syndrome, intraventricular hemorrhage, apnea, necrotizing enterocolitis) were significantly ($p<0.001$) associated with an increased risk ADR occurrence. Mechanical ventilation and total IV nutrition increased the risk of ADR; 3.6 and 5.4 ($p<0.001$) respectively. Hyperbilirubinemia (>12 or >15 mg/dl) was not a risk factor, but abnormal liver function (SGOT >100 units) increased the risk 9.6 fold. Abnormal kidney function (BUN >30 mg/dl, serum creatinine >1.2 mg/dl) also increased ADR risk 9 fold ($p<0.001$). We conclude that the sick low birth weight neonate receiving mechanical ventilation who has abnormal renal or liver function is at greatest risk for ADR.

● 319 POST-NATAL DEVELOPMENT AFFECTS THE CONTRACTILE RESPONSES TO CALCIUM (Ca) CHANNEL BLOCKERS Michael Artman, Thomas P. Graham Jr., Robert Boucek, Jr., Vanderbilt University, Nashville, TN

We previously observed a greater inotropic sensitivity to verapamil (V) in perfused hearts isolated from immature (I;14-21 day old) compared to adult (A) rabbits. Mechanisms for this difference were explored using right ventricular papillary muscles isolated from I and A rabbits (1.0 Hz; 30°C). Cumulative dose responses to V or nitrendipine (N) were obtained by measuring developed tension (DT), and dT/dt. The concentrations (μM;mean±SE) that reduced pre-treatment values by 50% are shown:

	Verapamil			Nitrendipine		
	50% DT	50% dT/dt	(n)	50% DT	50% dT/dt	(n)
I:	0.74±0.1	0.80±0.1	(7)	0.51±0.1	0.65±0.1	(6)
A:	5.1 ±0.8*	5.8 ±0.7*	(7)	1.4 ±0.3*	1.8 ±0.4*	(7)

*indicates I different than A, ($p<0.05$)

Because the normal force-frequency response reflects enhanced transarcolemmal Ca influx, this relationship was studied in each group in the absence and presence of V or N. V abolished the positive staircase in both groups. N depressed the positive staircase in the adult, but N augmented the positive staircase in the immature. These data indicate age-related differences in the manner in which Ca reaches the myofilaments, especially at higher rates. Furthermore, based on recognized differences in the mechanisms of action of V and N, our results suggest developmental differences in the relative contributions of sodium-Ca exchange and Ca channel influx to the Ca which participates in myocardial contraction.

320 POSSIBLE GROWTH IMPAIRMENT IN PUPS ON CHRONIC CONVERTING-ENZYME INHIBITOR. Susan P. Bagby, (Spon. by Robert C. Neerhout), Oregon Health Sciences University, School of Medicine, Portland, OR.

In 4 neonatally-coarcted dogs and 4 normal littermates, all males from an inbred colony, angiotensin converting-enzyme inhibitor (CEI: MK421) was given chronically (3 mg/kg po q 12h) from age 16±2 days (48h post-aortic banding) through 4-6 months of age. Clinically apparent substandard weight (wt) gain in all dogs prompted comparison of growth rates (linear regression of wt in kg on age in days) in the 8 CEI-treated dogs with those of 13 male historic controls (Cont-H) from the same inbred colony: 6 coarcted and 7 littermates studied over the same age range in prior years. Also, body wt in CEI-treated dogs at 6 months of age was compared with 6-month wt in a second group of concurrent controls (Cont-C): 8 normal male inbred-colony dogs born in the same year as CEI-treated dogs. Growth rates (slope of growth curve) and 6-month wt were compared by T-test. Results (mean ± SD) are:

	CEI	Cont-H	Cont-C
Growth Rate (kg/d)	.091±.017 (n=8)	.118±.023 (n=13)	-
6-Month wt (kg)	18±2 (n=8)	-	26±2 (n=8)

Both growth rate ($p<.01$) and 6-month wt ($p<.001$) were significantly lower in CEI-treated pups. Since the study was not designed to test MK-421 effects on growth, results cannot fully exclude litter-dependent factors. However, given the potential relevance to the use of CEI in pediatric populations, the possibility of growth impairment warrants further study.

† 321 125I-IODOCYANOPINDOLOL (ICP) BINDING TO NEWBORN RAT LIVER MEMBRANE J. Bendeck, A. Noguchi, (Spons. by Wm. Keenan), Dept. of Pediatrics, St. Louis University.

Rat liver glycogenolysis is stimulated by β-adrenergic mechanism in newborn (NB) but α in adult (AD). It has been speculated that this maturational change from β to α control is related to changes in numbers of plasma membrane (PM) receptors. However direct binding of β radioligands to NB liver had been unsuccessful. We examined a new β ligand ICP in binding assays with NB and AD liver PM and correlated with adrenergic stimulation of glycogen phosphorylase (GP) in isolated hepatocytes. PM was purified 7±1 times in NB and 11±2 times in AD assessed by 5'-nucleotidase. ICP binding was saturable, reversible and was displaced by Isop>Epi>Norepi and Alprenolol>>Metoprolol in both NB and AD. GTP lowered the Epi affinity of ICP binding sites similarly at both ages. The number of ICP (β) binding sites was contrasted with α_1-ligand, ^{3}H-Prazosin binding sites.

	n	wt	^{125}I-ICP(β) KD	^{125}I-ICP(β) βmax	^{3}H-Prazosin(α) KD	^{3}H-Prazosin(α) βmax
		grams	(pmol)	(fmol·mg^{-1})	(pmol)	(fmol·mg^{-1})
Newborn	5	12-16	30±2	114±4	103±7	161±14
Adult	5	195-265	31±5	19±3*	58±11*	554±59§

Means±S.E. *:Adult<Newborn, §:Adult>Newborn $p<.001$

GP was also stimulated by Isop>Epi>Norepi in NB hepatocytes. Inhibition of Epi stimulated GP was Alprenolol (A)>>Phentolamine (P) in NB and P>>A in AD. We conclude 1) liver ICP binding sites are β_2 subtype receptors and 2) the change in GP stimulation from β to α mechanism seen with maturation is related to changes in receptor number.

● 322 PHARMACOKINETICS OF EXOGENOUS VITAMIN E IN THE NEWBORN. R. BHAT AND R.J. BRAUN. (Spon. by D. Vidyasagar). Department of Pediatrics, University of Illinois at the Medical Center, Chicago, Illinois 60612.

These studies were designed to evaluate the pharmacokinetics of vitamin E following intravenous (IV), topical (TOP) as eye drops, and intramusclar (IM) vitamin E in the newborn kitten as the animal model of retinopathy of prematurity. TOP adminstration of E had no significant effect on tissue or plasma E concentration. The mean plasma concentration of E in the control and TOP treated animals was 0.5 mg%. Plasma levels of radiolabelled E following IV adminstration (100 mg/kg) decayed in a triphasic manner: the half-life of the inital component was 2 hrs while the terminal component half-life was 86 hrs. Plasma concentration of E during the first two hrs ranged from 70-80 mg% and therapeutic E concentration of 3 mg% was not observed until 48 hrs. after IV administration. Plasma values for E following IM administration (100 mg/kg) reached a steady state level of 5-7 mg% within four hrs and was maintained for up to 120 hrs. It is concluded that the IM route of administration provides an effective method for rapid introduction and maintenance of therapeutic vitamin E levels in the plasma of the newborn.(Supported in part by NIH EY04990).

† 323 RETINAL AND TISSUE VITAMIN E KINETICS IN THE NEWBORN KITTEN FOLLOWING VITAMIN E ADMINISTRATION. R. Bhat and R. J. Braun. (Spon. by D. Vidyasagar). Department of Pediatrics, University of Illinois Hospital, Chicago.

The effectiveness of vitamin E in prevention of oxygen induced tissue damage is likely related to the concentration at the site of action. The objective of this study was to evaluate the tissue disposition of E in the newborn following topical (TOP) as eye drops, intravenous (IV) and intramuscular (IM) E (100 mg/kg) . TOP E had no significant effect on serum or tissue levels of E. Peak E concentration in the liver and lung following IV was observed within 5 hrs; However maximal sustained retinal E levels following IV administration were not observed until 40 hrs. . IM administration produced a significant increase in retinal E within 16 hrs. Peak values for serum, tissue (mcg/g tissue) and retinal (mcg/g protein) E are:

	Plasma	Liver	Retina	Lung	Kidney	Brain
	mg %	mcg/g	mcg/g	mcg/g	mcg/g	mcg/g
Control	0.4	19.	10.	10.	7.5	4.2
IM	16.	1100.	220.	80.	90.	10.
IV	80.	1400.	130.	240.	47.	10.

We conclude (1) IM administration produced a more rapid and sustained increase in retinal vitamin E levels in comparison to IV administration; (2) whereas IV administration produced higher levels of vitamin E in the nontarget organs. (Supported by NIH EY04990).