379 PHARMACOKINETICS OF CEFTAZIDIME IN THE NEWBORN INFANT. A.G. James, K. Farmer, J. Aryton, C. Harrison, (Sponsored by P.R. Swyer), Department of Pediatrics, National Women's Hosp., Auckland, New Zealand.

Ceftazidime, a new parenteral broad spectrum cephalosporin, is stable to most β-lactamases and has high activity against Pseudomonas species, Providencia, Serratia and indole positive Proteus. Studies in adult human volunteers demonstrate high long lasting serum levels, low serum binding and high recovery of unchanged antibiotic in the urine, and have failed to reveal any evidence of toxicity. Sixteen newborn infants received treatment with intravenous Ceftazidime 30 mg/kg 12 hourly for suspected neonatal sepsis. The median gestational age of the infants was 32 weeks (range 26-42 weeks) and the mean birthweight 1700 grams (range 820-3520 grams). Pharmacokinetics of Ceftazidime were determined in the infants and serum concentration time curves were characterised by the two compartment open system kinetic model. The mean serum concentration 1 hour after the 30 mg/kg infusion was 38.95 mg/L and the mean serum trough level was 13.8 mg/L. Elimination half-lives correlated inversely with gestational age. The mean half lives during the first week of life were 5.0 hours in infants <32 weeks, 4.7 hours in those 32-37 weeks, and 3.3 hours in term infants. The drug was well tolerated and adverse effects were not observed.

● 380 EFFECTS OF A CALCIUM ANTAGONIST ON THE CARDIOVASCULAR (CV) RESPONSES TO AN α_1 ADRENOCEPTOR AGONIST IN DEVELOPING SWINE. Marisa Jarenwattanonon, Norman Gootman, Barbara J. Buckley, Nancy A. Kaplan, Peter G. Griswold, and Phyllis M. Gootman. SUNY Stony Brook, Schneider Children's Hospital, Dept. of Pediatrics, Div. of Pediatric Cardiology, New Hyde Park, N. Y.

This study examined whether verapamil (V) can block α adrenoceptors in newborns, as reported in adults (Bou, J. et al., J. Auton. Pharmac. 3: 219-232, 1983). CV responses to the α_1 agonist, phenylephrine (PE), given as an i.v. bolus (20 mcg/kg), were examined before and immediately after a 2 min i.v. infusion of 100 or 300 mcg/kg V in 28 anesthetized, 1 day and 2 week old piglets. ECG, heart rate (HR), aortic (AoP) and LV pressures, LV dP/dt max and phasic mesenteric (Mes), renal (Ren) and femoral (Fem) flows were recorded; vascular resistance (R) was calculated. PE increased mean AoP, MesR and RenR and decreased HR with no consistent changes in LV dP/dt max and FemR. In 1 day olds, there was no significant difference in CV responses to PE before and after V. In 2 week olds after high dose V, the following responses (mean % change ± SE) to PE were significantly diminished: MesR (174±58 vs 85±33; $p \leq 0.02$), RenR (246±41 vs 124±29; $p \leq 0.02$), mean AoP (54±6 vs 38±5; $p \leq 0.003$). The smaller increase in mean AoP elicited less of a reflex bradycardia. After low dose V the PE induced increase in LV dP/dt max was augmented (13±4 vs 22±4; $p \leq 0.04$), while the increase in RenR to PE was diminished in all 2 week olds. The results indicate that the ability of V to block α_1 adrenoceptors matures postnatally. This may be another manifestation of functional immaturity of α adrenoceptors at birth. The results of the present study provide a basis for understanding the age- and dose-dependent CV effects of V observed in young swine (Gootman, N. et al, Pediatr. Res. 18: 122A, 1984). Supported by Am. Heart Assoc., Nassau Chapter.

381 NEONATAL ABSTINENCE, PHARMACOTHERAPY, AND DEVELOPMENTAL OUTCOME, Karol Kaltenbach and Loretta P. Finnegan, Jefferson Medical College of the Thomas Jefferson University, Department of Pediatrics, Philadelphia, PA.

The majority of infants born to drug-dependent women undergo neonatal abstinence syndrome (NAS) and often require pharmocotherapy for the treatment of withdrawal symptoms. Phenobarbitol, paregoric, and diazepam have been recommended for the treatment of the syndrome. While some investigators have examined the efficacy of these agents in treating NAS, there are no data regarding the use of specific pharmacologic agents and developmental outcome. This study evaluated 85 infants born to drug-dependent women who were maintained on methadone during pregnancy. Severity of infant withdrawal was assessed with the Neonatal Abstinence Scoring system (Pediatric Research 7:319, 1973). Infants who required pharmacotherapy were randomly assigned to one of four treatment regimens: paregoric, phenobarbitol (titration), phenobarbitol (loading), and diazepam. When treatment was not successful with the assigned agent, one of the other agent(s) was used. At 6 months of age, the developmental status of infants was assessed with the Bayley Scales of Mental Development. Based on NAS treatment, four groups were delineated: I) paregoric (n=21); II) phenobarbitol (n=17); III) more than one agent (n=31); and IV) no treatment. (Data for the phenobarbitol loading and titration groups were combined since analysis revealed no differences between groups. All infants who initially received diazepam were included in Group III since diazepam as a single agent was not successful). Results of one way analysis of variance revealed no differences in developmental status between groups ($p = <.10$, $f=.25$). Scores for all groups were well within the normal range of development. Implications of these findings include, 1) the severity of withdrawal is not related to developmental outcome when appropriately managed with pharmacotherapy, and 2) the use of pharmacotherapy does not adversely effect the developmental outcome and may help ameloriate the consequences of NAS.

● 382 DECREASED FOLATE ASSOCIATED WITH METHOTREXATE POLYGLUTAMATE ACCUMULATION IN CHRONICALLY TREATED MONKEYS. B.Kamen, N.Winick, C.Lester, F.Baylis, J.Holcenberg. Depts. of Ped. and Pharmacol. Univ. of TX Health Sci. Center, Dallas, TX, Univ. of So. CA Los Angeles, Pediatric Oncol.Br. NCI.

Methotrexate (MTX) a mainstay of continuation therapy for acute lymphoblastic leukemia is associated with hepatic and neurotoxicity. The metabolism of MTX to polyglutamates (MTXGLUn), which have long intracellular halflives may be partially responsible for these toxicities. In an effort to model the pharmacodynamics of repetitive, low dose MTX and the folate deficiency previously shown in red cells and livers from patients, the tissue content of MTX and folate from monkeys treated for 1 yr with 50 mgMTX/m^2 was analyzed. In addition, the MTXGLUn profiles were also determined by HPLC and radioligand binding assay. The MTX content (pmol/g wet weight) of liver, kidney, brain, testes were 2817, 836 4.9 and 44 respectively. The folate content (pmol/g wet weight) of these same tissues was 11500, 4485, 32 and 474. Control values for folates were 31064, 6500, 286 and 1355 respectively. The predominant MTX derivative(s) found were MTXGLU3-5 but GLU6-7 were easily detectable. Of special interest was the significant folate deficiency found in the brain (90% loss compared to control). Since inborn errors of folate metabolism often present with severe neurological problems not unlike those associated with MTX toxicity (including cerebral calcifications), the biochemical abnormalities associated with repetitive, low dose MTX therapy and its attendant folate deficiency may be responsible for the observed toxicity.

Supported by ACS CH228, a scholar award of the Leukemia Society of America, and the NCI.

383 DISPOSITION OF THEOPHYLLINE AND CAFFEINE IN NEONATAL PIGLETS. Gregory L. Kearns, Donald E. Hill, Bonnie J. Taylor, and Joanne S. Szabo, Univ. of Arkansas for Med. Sci., Dept. of Pharmaceutics and Pediatrics, Little Rock.

A pharmacokinetic (PK) study to evaluate the piglet as a model for theophylline (T) and caffeine (C) disposition was undertaken in 28 animals who received a 10 mg/kg IV bolus injection of C or T, followed by multiple blood sampling over 24 hours. C and T were quantitated from serum by HPLC (CV<3% at 0.1-100 mg/L). Comparison of T and C disposition was performed at 2 (n=6 per group), 4-5 (n=4 per group) and 19-20 (n=4 per group) days of age, and resulted in the following data (mean):

Age (d)	β(1/h) T	β(1/h) C	$T_{½\beta}$(h) T	$T_{½\beta}$(h) C	Vd_{area}(L/kg) T	Vd_{area}(L/kg) C	CL(L/kg/h) T	CL(L/kg/h) C
2.0	0.026	0.005	28.33	155.89	0.62	1.05	0.016	0.005
4.25	0.054	0.016	13.00	49.12	0.71	1.02	0.038	0.016
20.25	0.118	0.049	6.10	14.70	0.60	0.76	0.073	0.038

With the exception of T clearance (CL) between the 4.25 and 20.25 day groups, and Vd_{area} for all age groups, there were significant ($p<0.05$) differences for C and T PK parameters between all age groups. C was not detectable in piglets receiving T; however, T was detected (0.4±0.2 mg/L at 11.5±4.2 hr) in the 4 oldest piglets receiving C. PK parameters for C and T in piglets studied at 2 days of age were similar to those reported in human neonates. In the older animals, they were markedly different than values reported for human neonates of similar age. Furthermore, ability for T biotransformation to C appears deficient in the piglet. These differences from human neonates will require further elucidation for piglets to be effective "models".

384 ANTIOXIDANT PROPERTIES OF PHARMACOLOGIC DOSES OF VITAMIN E IN NEWBORN RABBITS. Matthew E. Knight, Jon R. Wispé and Robert J. Roberts, Depts. of Pediatrics and Pharmacology, Coll. of Med., Univ. of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Studies of pharmacologic doses of vitamin E in our laboratory have shown that dosage form and route of administration influence the level and predominant form of vitamin E present in tissue. The functional significance of the quantity and predominant form of vitamin E in tissue was assessed by measurements of antioxidant activity in lung tissue resulting from IV administration of T or TA. One-day-old rabbits were given 0, 1, 10 and 100 mg/kg T or TA IV. The lungs were removed, and a portion was saved for later HPLC analysis of vitamin E content. The remaining lung was homogenized and incubated with an Fe/ascorbate system to generate lipid peroxidation (LP). After 30 min, the reaction was stopped with EDTA; and LP was quantitated using a TBA-based method which measures malonaldehyde (MDA). Increasing IV doses of T resulted in increasing T levels in lung and a comparable lowering of LP (Dose:1 mg/kg, T level 19 ± 5 mcg/g, MDA 203 ± 38 nmoles/g; Dose:100 mg/kg, T level 1901 ± 572 mcg/g, MDA 52 ± 24 nmoles/g). TA given IV increased lung TA levels, but no reduction in LP was observed (Dose:1 mg/kg, TA level 90 ± 68 mcg/g, MDA 297 ± 122 nmoles/g; Dose:100 mg/kg, TA level 1140 ± 548 mcg/g, MDA 281 ± 139 nmoles/g).

In a defined in vitro oxidant stress sytem, T elicits a dose-related antioxidant effect. TA administration increased lung TA content but did not result in a significant reduction in LP. TA given IV appears to lack efficacy as an antioxidant in the lung.