348 IMPACT OF DRUG DEPENDENCY DURING PREGNANCY ON NEONATAL MORPHOMETRICS. Stephen R. Kandall, Tatiana M. Doberczak, Sylvain M. Weinberger, Wolfram Loewenstein, John C. Thorton, Jonine L. Bernstein (Spon. by Walter L. Henley) Depts of Pediatrics, Beth Israel Medical Center & Biostatistics, Mt. Sinai School of Medicine, New York.

The impact of maternal drug dependency on neonatal morphometrics was studied in 150 mother-infant and 150 concurrent control pairs. The maternal population included 121 methadone-maintained women, of whom 80 abused other drugs concomitantly; the remaining 29 women used multiple street drugs. Mean birth weight of the passively addicted neonates(PA)(2.80 kg ± 0.55)(SD) differed significantly from controls(C)(3.25 kg ± 0.59)($p < .001$). Mean head circumference of PA infants(32.6 cm ± 1.8)also differed significantly from C(33.8 cm ± 1.7)($p < .001$). Mean weight and head circumference of PA newborns fell at the 25th percentile for gestational age, differing from the C group value(50-75th percentile)($p < .001$). Mean gestational age(PA 38.9 wks ± 2.2 vs C 39.3 wks ± 2.3) and prematurity rates(10% PA vs 7% C)did not differ, but IUGR was increased to 20% in the PA group vs 4% C($P < .001$). Within the PA group, selected perinatal variables of maternal age, parity, weight gain during pregnancy, polydrug abuse, methadone dosage, and duration of drug and alcohol use were not significantly associated with either birth weight or head circumference.

This demonstration of symmetrical IUGR in PA infants and the known association of small head size at birth with reduced neurobehavioral outcome mandates greater concern for "optimal" methadone maintenance during pregnancy.

● 349 DISPOSITION OF PHARMACOLOGICAL DOSES OF VITAMIN E IN NEWBORN RABBITS. Matthew E. Knight and Robert J. Roberts. University of Iowa College of Medicine, University of Iowa Hospitals and Clinics, Departments of Pediatrics and Pharmacology, Iowa City, IA.

To study the effect of vitamin E dosage form and route of administration on tissue levels of vitamin E, newborn rabbit pups were given 100 mg/kg/day of α-tocopherol (T) or α-tocopherol acetate (TA) sc, po, and iv. Various tissues were obtained on days 1, 3, and 6 of life and analyzed for T and TC using HPLC. (All values represent mean ± SD, μg/g tissue, n=3-5). T levels in lung 1 day after T dosing were 36 ± 9 (sc), 13 ± 4 (po), and 92 ± 16 (iv); liver levels were 493 ± 110 (sc), 138 ± 73 (po), and 1362 ± 570 (iv). T tissue levels 1 day after sc TA administration were no different than controls (all ≤ 8 μg/g). T tissue levels 1 day after po and iv administration of TA were 18 ± 8 (po) and 79 ± 47 (iv) for lung and 253 ± 36 (po) and 10 ± 5 (iv) in liver. No TA was seen in tissues after po TA administration. In contrast, iv administration of TA resulted in tissue levels of TA at 1 day of 3957 ± 2589 in lung and 48 ± 30 in liver. T and TA tissue levels after 3 and 6 days of daily dosing with T or TA were similar to the 1-day data in distribution although increased in amount. From the results, we conclude that T given parenterally or orally results in marked increases in T tissue levels; whereas parenteral TA administration does not increase T tissue levels. Extensive hydrolysis of TA to T occurs with po administration of TA, but only minimal hydrolysis occurs with parenteral routes of administration. When given parenterally, TA may be ineffective as an antioxidant. (Supported in part by NIH GM12675.)

● 350 UNEXPECTED ABNORMALITIES OF FENTANYL (F) DISPOSITION IN CHILDREN UNDERGOING CARDIAC SURGERY. Gideon Koren, Gerald Goresky, Peter Crean, Julia Klein, Stuart MacLeod. Depts. of Pediatrics and Anesthesia, The Hospital for Sick Children, Toronto, Canada.

F is a useful anesthetic in cardiac surgery; however, an optimal F dosage for children has not been defined on the basis of pharmacokinetic analysis. We studied 19 patients (5 mo-16 yr) at cardiac surgery with cardiopulmonary bypass (CPB). An F bolus of 50 or 30 mcg/kg was given over 30 sec. with concomitant initiation of F continuous infusion at a rate of .15 or .3 mcg/kg/min. F plasma concentrations of 30 minutes were up to 3-fold higher than reported with similar regimens in adults. The calculated mean values for $T_{\frac{1}{2}\alpha}$ (10.2 min); $T_{\frac{1}{2}\beta}$ (102 min); and TBC (13.3 ml/kg/min) were close to adult whereas the mean Vdss (1.2 L/kg) was significantly lower. There was a positive correlation between age and Vdss ($r=0.85$; $p<0.01$), and a negative correlation between age and TBC ($r=-0.73$, $p<0.05$. Following the commencement of CPB there was a 74% mean decrease in F levels, much greater than would have been expected from hemodilution alone. Sequestration of F by the CPB with binding to both the membrane oxygenator (major) and to the siliconized tubing (minor) accounts for much of the steep decrease in F levels. During CPB and hypothermia F concentrations remained low but stable probably reflecting a significant reduction in hepatic metabolism of F. Our data suggest an optimal pediatric F dose of 30 mcg/kg given as a bolus combined with an infusion of 0.3 mcg/kg/min throughout surgery.

† 351 CHARACTERISTICS OF DIGOXIN INTERACTION WITH QUINIDINE, VERAPAMIL AND AMIODARONE: IN VIVO AND IN VITRO STUDIES. Gideon Koren, Stuart MacLeod, Div. Clin. Pharmacology: Hospital for Sick Children, Toronto, Canada.

Recently several drugs which are commonly coadministered with digoxin have been shown to cause toxic accumulation of the cardiac glycoside. The interactions with quinidine and verapamil have been attributed in part to reduced renal clearance of digoxin. Since GFR is not altered it appears that renal tubular secretion of digoxin must be inhibited. We studied the effect of amiodarone on serum digoxin concentrations (SDC) in 10 children aged 0.5-18 yrs. There was a 68-800% increase in SDC ($P < .025$) when both drugs were used in normally recommended doses. Digoxin renal clearance was reduced by 10-44% without corresponding alteration in creatinine clearance. A similar interaction was demonstrated in rats. The addition of amiodarone 30 mg/kg/day caused SDC to increase from 0.68±0.08 (mean ± SD) to 11.22 ± 2.16 ng/ml ($P<0.005$). Subsequent studies in vitro have examined the effect of quinidine, verapamil, and amiodarone on the uptake of ^{125}I digoxin in renal cortical slices of rats. Therapeutic concentrations of quinidine (5 ug/ml), verapamil (500 ng/ml), and amiodarone(2 ug/ml) caused significant inhibition of digoxin uptake by renal slices (26%, 15%, and 16% respectively) ($P<.01$). Quinidine and verapamil were shown to cause further dose-dependent inhibition of digoxin uptake. These studies support the suggestion that elevated SDC is induced by reduction in the tubular secretion of digoxin caused by quinidine, verapamil, and amiodarone. Whenever these drugs are added to digoxin therapy, follow-up assessment of SDC is mandatory.

352 FAILURE TO ACHIEVE THERAPEUTIC ACETYL SALICYLIC ACID (ASA) CONCENTRATIONS IN CHILDREN WITH KAWASAKI DISEASE (KD). Gideon Koren, Stuart MacLeod, Div. of Clin. Pharmacol., The Research Institute, The Hospital for Sick Children, Dept. of Pharmacology and Pediatrics, University of Toronto, Toronto, Canada.

ASA is the most widely used drug in KD. Several studies have demonstrated that satisfactory reversal of clinical symptoms and signs is achieved only after dosage in excess of 100 mg/kg/day. Low dose ASA treatment has been shown ineffective in prevention of coronary aneurysm formation. We retrospectively assessed 49 children (33 m:16 f) aged 2.6 ± 1.8 yrs (range 8 mo-8 yrs) who had KD and were treated with ASA 30-180 mg/kg/day. There was a good correlation between dosage and salicylate concentrations ($r=0.69$; $p<0.001$); however, wide variability existed. At dosage below 80 mg/kg/day no ASA serum concentration exceeded 20 mg/dl. In children receiving 100-110 mg/kg/day, 55% of the serum concentrations were below 20 mg/dl. A similar pattern was seen with doses >120 mg/kg/day; however, 28% of levels were above 30 mg/dl. Although there was no evidence of major salycilate toxicity in the group, 3 children receiving >100 mg/kg/day had ASA-induced gastritis. In 11 children significant day to day fluctuation in concentrations was seen. Erratic absorption of ASA was demonstrated in an additional 3 children with KD (age 7-24 mo), studied prospectively. Only 14-20% of their daily ASA dose was recovered in 24 hr urine (normal 80-90%). Serum ASA concentrations were subtherapeutic. The high ASA dose needed to overcome impaired absorption should be accompanied by careful monitoring because of unpredictable absorption changes.

353 IS CONVENTIONAL DOSAGE FOR AMIKACIN(A) SAFE FOR VLBW INFANTS? Isabel Kurlat, Cristina Couceiro, Jorge Urman Augusto Sola. University of Buenos Aires School of Medicine, Hospital de Clinicas, Neonatology Section, Department of Pediatrics. Buenos Aires, Argentina. (Spon by George A. Gregory)

The recommended dose of A for newborn infants(7.5mg/kg q 12 h) has not been thoroughly evaluated in the VLBW infant. In order to determine whether this dose is adequate to achieve therapeutic and safe serum concentrations in VLBW infants, we measured A levels by RIA in 8 infants(wgt $\bar{X}$:1100, range 750-1500; gest.age $\bar{X}$:30, range 27-33 wks). Blood for Peak Levels(PL)(Normal 15-25 mcg/ml) was obtained 1 hour after IM doses 1,2,3,6 and 14, and for Trough Levels(TL)(Normal 4-8 mcg/ml)immediately before each IM dose. After dose 1, the 8 infants had PL within therapeutic range. All samples obtained for PL(40) were ≥15mcg/ml. Of the 40 PL, 24(60%) were ≥25 mcg/ml and 17(42.5%)were actually ≥35 mcg/ml. For IM dose 14(7^{th} day of treatment), 6(75%) of PL were ≥40 mcg/ml.
None of TL were <4 mcg/ml. Of the 40 TL, 24(60%) were >8 mcg/ml and 19(47.5%) were actually >15 mcg/ml. From IM dose 3, all TL were greater than 8 mcg/ml.
These data indicate that 7.5 mg/kg is an adequate amount of A for VLBW infants. However, the 12 hours dosing interval causes accumulation of the drug to potentially toxic levels in all cases making this interval unsafe. We are now evaluating pharmacokinetics of A, and a new dose regime. Until further data is available we suggest that A should be given every 18 to 24 hours in the VLBW infant, in order to avoid undesirable high levels.