PHENYTOIN KINETICS IN NEWBORNS.

- **317** Blaise P.D. Bourgeois and W. Edwin Dodson, Wash. Univ., St. Louis Children's Hospital, Dept. of Ped. and Neurol., St. Louis, MO.

To determine the relative contribution of age and absorption on phenytoin (PHT) kinetics in full-term newborns, we measured PHT apparent half-life ($t_{50\%}$) 15 times in 9 infants aged 2 to 36 days. PHT was given i.v. 9 times and p.o. 6 times. The PHT $t_{50\%}$ ranged from 140 hours in a 2 day old to 3.78 hours in a 36 day old. Whereas the $t_{50\%}$ correlated directly with initial concentration (C_1) in the 8 patients ≥ 9 days old ($r=0.755$, $p<.05$), there was no correlation in 7 younger patients. $t_{50\%}$ varied inversely with age, averaging 84.7 hr (SD 42.6) in patients less than 8 days old and 14.7 hr (SD 7.74) in older patients ($t=4.59$, $p<.01$). Controlling for the effect of C_1 , the average $t_{50\%}$ was still reduced by more than 3 times in the older group (84.7 vs 25.5 hr, $p<.02$). Preliminary study of PHT absorption suggests that the reduction of PHT levels seen in infants more than 1 week old is even greater than predicted by this 3-fold increase in PHT eliminatory capacity and supports the notion that PHT bioavailability is significantly reduced in infants.

Thus, the relation between C_1 and $t_{50\%}$ of PHT changes rapidly during the first month of life, a change which must be considered when studying PHT administration and absorption in newborns. For an individual newborn these kinetic changes are unpredictable and repeated PHT measurements are essential.

- **318** RISK: BENEFIT CONSIDERATIONS FOR THE SAFE USE OF ISOXSUPRINE IN THE TREATMENT OF PREMATURE LABOR Jane E. Brazy, Virginia Little, Judy Grimm, and Marcos Pupkin (Spon. by G.W. Brumley), Duke University Medical Center, Dept. of Pediatrics, Durham, NC.

Seventy consecutive patients treated with isoxsuprine for premature labor were studied to determine pregnancy factors associated with tocolytic success, the extent of placental drug transfer, and time course of therapy in order to define conditions which would maximize success and minimize acute neonatal isoxsuprine toxicity. In patients with intact membranes, successful prolongation of pregnancy >7 days occurred in 77% of women with $\leq 50\%$ cervical effacement and ≤ 3 cm dilatation at the initiation of therapy, and in none with $>50\%$ effacement and >3 cm dilatation. Cervical effacement was the primary factor in determining success. Cord isoxsuprine concentrations averaged 90% of maternal concentrations at delivery. Maternal and cord isoxsuprine concentrations at delivery were inversely correlated with the drug-free interval before delivery. An interval >5 hours was necessary to attain a cord concentration of <2 ng/ml, a level not associated with neonatal problems. Drug-free intervals ≤ 2 hours usually resulted in cord isoxsuprine values >10 ng/ml, levels associated with severe neonatal problems. Since 17 of the 22 infants with cord isoxsuprine concentrations >2 ng/ml and eight of nine with values >10 ng/ml were delivered of mothers with >3 cm dilatation or $>50\%$ effacement at the initiation or reinstitution of intravenous therapy, most severe neonatal drug-level related problems are preventable.

- 319** USE OF TRANSCUTANEOUS PCO_2 ELECTRODES FOR DIAGNOSIS AND THERAPY OF INFANTS IN SHOCK. Luis A. Cabal, Antonio Gomez, Hernan Cruz, Sze-ya Yeh, Joan E. Hodgman, Bijan Siassi, Univ. of So. Calif. Sch. of Med. LAC/USC Medical Center, Dept. of Peds. Los Angeles, California

Transcutaneous PCO_2 (Ptc CO_2) values are dependent on changes of local perfusion. We studied the effects of shock, acidosis and cardiovascular (CV) drugs on unheated (NH) Ptc CO_2 in 21 preterm and 5 term infants who required dopamine (D), isoproterenol (I), tolazoline (T) and transfusions of blood (B). Simultaneous Pa CO_2 and NHPtc CO_2 tensions obtained before and during drug therapy were compared. Correlations of values obtained during hypotension (BP $<2SD$ of normal), acidosis (pH <7.25) or both treated with CV drugs, were compared to those during the same conditions without CV drug therapy. When CV drugs were not given, Ptc CO_2 values during hypotension were the highest and most discrepant from Pa CO_2 . Administration of I and D decreased the Ptc CO_2 differences. With CV drugs, the differences became greater in hypotension accompanied by acidosis. T and B decreased the difference between Ptc CO_2 and Pa CO_2 . These data suggest that: 1) The high Ptc CO_2 associated with cardiovascular compromise reflects lack of tissue perfusion. 2) In hypotension, widened Ptc CO_2 - Pa CO_2 differences are narrowed by CV drugs. 3) If acidosis is added to hypotension, CV drugs are less effective in reducing the differences, suggesting it interferes with their action. 4) T and B narrow the differences, indicating improved tissue perfusion. We conclude the Ptc CO_2 electrode can be valuable as an indicator of tissue perfusion in the care of infants with cardiovascular alterations.

- **320** PLACENTAL TRANSFER AND FETAL ELIMINATION OF MORPHINE Martin S. Cohen, Lewis B. Sheiner, Leslie Z. Benet and Abraham M. RUDOLPH, Univ. of Calif. Dept. Ped. San Francisco

Placental transfer of morphine (M) was studied to determine: 1) the rate of transfer of M across the placenta; 2) the degree that the fetus is responsible for its own elimination of M; 3) the selective directional clearance of M across the placenta. We placed chronic catheters in the descending aorta and inferior vena cava (IVC) of six pregnant ewes and their fetuses, and into the uterine (UTV) and umbilical (UMV) veins. Electromagnetic flow transducers were placed around the common uterine (UTA) and umbilical (UMA) arteries. M was infused into the maternal IVC at 15.8 mg/hr until steady state conditions were achieved. UTA, UTV, UMA, UMV M concentrations and UTA and UMA blood flows were measured at 5 and 6 hours. The next day, M was infused into the fetal IVC at 3.28 mg/hr and the same procedure followed. RESULTS: Maternal Infusion- The rate of intrinsic loss of M by the mother was 15.73 mg/hr or 99.6% of the infusion rate. The rate of loss of M from the mother to the fetus was 0.06 mg/hr or 0.4% of the infusion rate. Fetal Infusion- The rate of intrinsic loss of M by the fetus was 2.44 mg/hr or 74.4% of the infusion rate. The rate of loss of M from the fetus to the mother was 0.84 mg/hr or 25.6% of the infusion rate. There was no significant difference between maternal to fetal (1386 ml/hr) and fetal to maternal (984 ml/hr) clearances of M. Thus, 1) the rate of M transfer from the mother to the fetus is low relative to the infusion rate and the fetus is not a significant route of elimination of M by the mother; 2) the fetus is primarily responsible for elimination of M entering its circulation; and 3) there is no selective clearance of M across the placenta in either direction. Supported by NIH grants DA02280 and GM26691

- **321** ECHOCARDIOGRAPHIC EFFECTS OF INTRAUTERINE ISOXSUPRINE EXPOSURE. Carolyn Crawford, Frank Bowen, Jr., Vinod Bhutani and Mary LuAnn Hall (spon. by Alfred Bongiovanni), Dept. of Peds., Univ. of Pa., School of Med., Penna. Hosp., Phila. Septal hypertrophy is seen in IDM who are hyperinsulinemic secondary to maternal hyperglycemia. The ventricular septum has increased numbers of insulin receptors. Isoxsuprine (ISX) has been reported to cause increased cord blood insulin. To demonstrate whether an association between ISX exposure, hyperinsulemia and ASH occurred Echocardiography (EC) was performed on 30 infants who had ISX exposure and 25 control infants. Normal septal thickness is 3-4 mm.

	Gest Age	BW	Apgar	Days of ISX	Cord Blood Insulin
Cont	32.9 $\pm$ 3.57	1577 $\pm$ 493	7.4 $\pm$ 2.5	.75 $\pm$.88	15.5 $\pm$ 5.7
ISX	33.9 $\pm$ 3.99	2094 $\pm$ 825	7.8 $\pm$ 1.4	16.4 $\pm$ 24	27.0 $\pm$ 18.9
P	NS	.01	NS	.005	.005

The control septal thickness was .38 $\pm$.04. The ISX septal thickness was .55 $\pm$.13. These are significantly different at $p < .005$.

The ISX treated infants were larger, had thicker ventricular septae and had higher cord insulin levels than non or partially treated controls. ISX as a tocolytic agent may have a similar effect on the fetus as maternal diabetes.

- 322** IN UTERO ISOXSUPRINE EXPOSURE: ANATOMIC AND BIO-CHEMICAL CHANGES IN NEONATAL RATS. Carolyn Crawford, Stephanie Boggs, and Christopher Neff (Spon. by Alfred Bongiovanni), U. of Pa. Sch. of Med., Pa. Hosp., Dept. of Peds., Phila., Pa. Isoxsuprine (ISX) treatment of premature labor has been associated with diverse metabolic side effects including hypoglycemia. This study was designed to identify anatomic and biochemical changes associated with ISX exposure during pregnancy. 6 timed-pregnant rats received ISX at 2mg/Kg/day at 120, 96, 72, 48 and 24 hrs. prior to delivery. 4 timed-pregnant control rats received similarly timed saline placebo. 102 neonatal rats were analyzed within 12 hrs. of birth. The results showed:

Body Wt. (BW) (gm)	Liver (mg)	Heart (mg)	Kidney (mg)	Lung (mg)
Cont 6.10 (41)*	290.56 (41)*	29.11 (41)*	29.84 (32)*	119.45 (32)*
ISX 6.89** (61)*	287.85 (61)*	35.54** (61)*	33.54** (30)*	141.57** (47)*

Liver Glycogen (Glucose, mg/dl)	Liver/BW	Heart/BW	Kidney/BW	Lung/BW
Cont 204.4 (30)*	.048 (41)*	.0047 (41)*	.0048 (32)*	119.45 (32)*
ISX 128.9** (29)*	.041** (61)*	.0051** (61)*	.0047 (30)*	141.57** (47)*

The data confirm a significant effect of prenatal ISX on total BW, liver glycogen, heart/BW, liver/BW and organ weights of heart, kidney and lung and suggest that decreased hepatic glycogen may be a factor in neonatal hypoglycemia.

*=N **= $p < 0.005$