**323** PLACENTAL TRANSFER OF FENTANYL IN SHEEP. J. H. Eisele, Jr., B. W. Goetzman, J. M. Milstein, R. G. Wright, S. H. Bennett, R. W. Martucci. Univ. of Ca., Davis, School of Med., Dept. Anesthesia and Pediatrics.

Fentanyl citrate, a potent short activity narcotic is being considered for obstetrical analgesia/anesthesia. Fentanyl is highly protein bound (67%) and very lipid soluble (N-haptane 22), the latter suggesting rapid placental transfer of the unbound drug. We evaluated the kinetics and placental transfer of Fentanyl in 5 chronically catheterized pregnant ewes (near term) and their fetuses following intravenous injection of Fentanyl (4 µg/kg). Fentanyl was measured in serial blood samples from maternal arterial (MA) blood and fetal umbilical arterial (UA) and venous blood (UV) by radioimmunoassay. Similar kinetic studies were performed in 5 newborn lambs.

Preliminary analysis of Fentanyl concentrations in MA blood indicate a tri-compartmental washout with a rapid $\alpha t_{\frac{1}{2}}$ (2-4 min) and a slow $\gamma t_{\frac{1}{2}}$ (hrs). Newborn lambs exhibited similar kinetics. Fentanyl was present in UV blood for 5-10 min following maternal injection, but only at UV/MA ratios of less than 0.16, and it was usually not detectable in fetal arterial blood. No changes in maternal or fetal heart rate, blood pressure, or blood gases occurred during Fentanyl administration.

Our data indicate that Fentanyl levels in fetal sheep, following maternal administration of dosages that would be analgesic for humans, should be insignificant. Fentanyl appears to have significant potential for obstetrical usage.

**● 324** ROLE OF ENDOGENOUS FACTORS IN POST-NATAL DEVELOPMENT OF HEPATIC MICROSOMAL OXIDATIVE METABOLISM IN THE RABBIT. Michael A. Evans, Rama Bhat, Chris Papazafiratou and Dharmapuri Vidyāsāgar. Departments of Pediatrics and Pharmacology, University of Illinois Medical Center, Chicago, IL 60612.

Indomethacin (I) undergoes both microsomal oxidation to desmethyl-indomethacin (DMI) and cytosolic deacylation to desbenzoylchloro-indomethacin (DBI). The in vitro postnatal development of these two pathways was examined in the rabbit liver using collagenase-isolated hepatocytes and liver fractions incubated with 0.5 mM $^{14}$C-I and appropriate cofactors for drug metabolism activity. Samples were removed at 5 to 15 min intervals for analysis of I metabolites. Deacylation of I to DBI in the 10,000g liver homogenate increased rapidly during the 1st 2 wks after births and demonstrated adult values within day 12 of postnatal age. Results from freshly isolated hepatocytes were very similar to the 10,000g liver homogenate in the pattern of postnatal development of the DBI pathway. Oxidative demethylation of I to DMI in the 10,000g homogenate and isolated cells demonstrated a significant increase only after day 14 of postnatal age and demonstrated only 83% of adult value by day 32 of postnatal age. The isolated microsomal fraction demonstrated a significant postnatal increase in DMI formation during the first 2 wks of postnatal life and reached adult values within day 32 of postnatal age. It is postulated that the difference in postnatal development of I metabolism to DMI between isolated microsomes and the 10,000g homogenate or the isolated hepatocyte is due to endogenous substrates which are competitive for oxidative drug metabolism.

**325** PENTAZOCINE: EFFECTS ON PREGNANCY AND THE NEONATE. Loretta P. Finnegan, Ronald J. Wapner. Thomas Jefferson University Hospital, Departments of Obstetrics/Gynecology and Pediatrics, Philadelphia, Pa.

The effects of heroin addiction on pregnancy and the newborn have been profound. With the decrease in quantity and quality of heroin, women have begun to use other psychoactive agents such as pentazocine. Two groups of pregnant women enrolled in a comprehensive prenatal addiction program were studied: Group A (N=14) whose major drug of abuse was pentazocine; Group B (N=26) were maintained on methadone. Maternal and infant morbidity were compared. In Group A one mother and infant died. Differences were observed in the following parameters:

| | Group A | Group B | |
|---|---|---|---|
| Maternal complications (%) | 71 | 40 | |
| Infant complications (%) | 84 | 27 | |
| Neonatal abstinence therapy ($\bar{x}$ days) | 22 | 33 | t=1.309; N.S. |
| Birthweight ($\bar{x}$ grams) | 2345 | 2922 | t=3.199;p<.01 |
| Gestational age ($\bar{x}$ weeks) | 37 | 39 | t=2.338;p<.05 |
| LBW incidence (%) | 84 | 19 | |
| SGA incidence (%) | 62 | 4 | |
| AGA/LBW incidence (%) | 23 | 15 | |

No differences were seen in maternal age, gravity, abortions, obstetrical complications, or newborn Apgar scores. Neonatal abstinence symptoms occurred in all infants, and 85% of each group were treated. These data suggest that greater maternal and infant morbidity occur when pentazocine, as compared to methadone, is used during pregnancy.

**326** TRANSPLACENTALLY ACQUIRED XANTHINES IN APNEA OF PREMATURITY. Dennis M. Fisher, Marie Ragni, Maria Delivoria-Papadopoulos, Departments of Anesthesia, Clinical Pharmacology and Neonatology, Hospital of the University of Pennsylvania and The Children's Hospital of Philadelphia

Theophylline (T) and Caffeine (C) cross the placenta easily. Because of the ubiquity of xanthines in the maternal diet, we have examined the role of transplacentally acquired xanthines in apnea of prematurity. We studied 27 infants, 25-35 weeks gestation, without RDS, hyperbilirubinemia or sepsis. Group 1 consisted of 9 who developed apnea within one week of life. Group 2, 18 non-apneic infants, served as controls. Serum T and C concentrations were measured by HPLC at birth and daily for 7 days or until the onset of apnea. Group differences in birth weight and gestational age were eliminated by analysis of covariance.

BIRTH AND TROUGH THEOPHYLLINE AND CAFFEINE LEVELS (mcg./ml.)

| | T Birth | T Min. | C Birth | C Min. |
|---|---|---|---|---|
| Group 1 (Apnea) | 0.2±1.4 | 0.2±0.1 | 0.3±0.6 | 0.2±0.2 |
| Group 2 (No Apnea) | 0.5±0.1 | 0.1±0.2 | 0.3±0.8 | 0.1±0.4 |

There was no difference ($p>0.3$) between groups in birth levels of T, C, or T+C (the sum of T and C). In addition there was no difference ($p>0.3$) for T, C, and T+C between Group 1 at the onset of apnea and trough values from Group 2. These data suggest that transplacentally acquired xanthines play no role in apnea of prematurity.

**327** GENTAMICIN DISPOSITION IN ASPHYXIATED NEWBORNS: RELATIONSHIP TO MEAN ARTERIAL PRESSURE AND URINE OUTPUT. Charles Friedman, Bruce Parks, and John Rawson. (Spon by Arnold Smith) Dept of Pediatrics, Uni of Miss Medical Center, Jackson MS

Auto-regulation of renal blood flow (RBF) and glomerular filtration may be severely compromised in newborns following asphyxia. GFR and urine output may be more dependent on changes in mean arterial pressure (Pa) in the asphyxiated infant. Therefore, the disposition of aminoglycosides, which depend on GFR for clearance, may be altered.

27 preterm infants (<35 weeks gestation) with suspected or proven sepsis were prospectively studied. Gentamicin half-life (T1/2) was compared with the following factors: asphyxia, hypotension, and the use of dopamine (5-15ugms/kg.min) after volume expansion.

T1/2 is prolonged in asphyxiated infants (12.6 hrs vs 7.2 hrs $p=0.05$). T1/2 is not altered by the use of dopamine. In asphyxiated infants (N=8) the gentamicin T1/2 correlated with urine output ($r=0.57$) and with Pa ($r=0.69$). These correlations are not present in non-asphyxiated infants. The gentamicin peak and trough values did not correlate with serial urine flow, blood urea nitrogen or creatinine. There is an inverse relationship to gestational age and post-natal age.

Following perinatal asphyxia, auto-regulation of GFR and RBF may be decreased so that gentamicin T1/2 is more dependent on Pa. Gentamicin kinetics should be carefully monitored in asphyxiated infants.

**328** THEOPHYLLINE METABOLISM BY THE HUMAN PREMATURE INFANT Lorne K. Garrettson, John L. Noles, Gilberto E. Rodriguez, Virginia Commonwealth Univ., Medical College of Va.,Depts of Pediatrics and Pharmacy, Richmond, Va.

The excretion of theophylline and its metabolites was studied in 8 premature infants treated for apnea. Changes and differences in metabolic patterns were sought. Theophylline and metabolites were assayed in urine and serum by HPLC. Urine was passed through a Dowex-2 column for clean-up prior to injection. Recovery of compounds by this method was >95%. In 6 patients, multiple 6 hour urine specimens were assayed.

Theophylline accounted for 62% of the total drug and metabolites excreted. The range was 54 to 95%. 1,3 dimethyluric acid (13DMU), the predominant metabolite in adults, accounted for 22% of the excreted drug. 1-methyluric acid and 3-methylxanthine comprised the remainder, although caffeine was not quantitated.

In 3 patients, there was a shift to a larger percentage excretion of 13DMU during therapy suggesting a development of metabolizing capacity. Dosage change in one patient resulted in no change in metabolite pattern.

Differences between patients may be the result of genetic variability or prenatal xenobiotics for which information was incomplete in this study.