NALOXONE(Nal) POTENTIATES THE PLASMA CATECHOLAMINE(CA) RESPONSE TO ASPHYXIA IN THE FETUS

●386 Alan B. Lewis, Mahvash Sadeghi. University of Southern California School of Medicine, Childrens Hospital of Los Angeles, Division of Cardiology, Los Angeles.

The effect of endogenous opioid peptide(EOP) blockade with Nal on the plasma CA response to asphyxia (hypoxemia+acidemia) was investigated in 6 chronically catheterized late gestation(>120 days) fetal lambs in utero. Animals were assigned randomly to receive either naloxone(1mg/kg) or saline on alternate days. Umbilical cord compression-induced hypoxemia(PO_2<15 torr) was maintained for 15 minutes and resulted in the development of acidemia(pH<7.30) after 10 minutes. Fetal HR declined initially and then increased progressively to approach but not return to baseline, whereas BP continued to rise throughout the 15 minute observation. No difference was noted between control and Nal-treated fetuses in their blood gas or cardiovascular responses. Plasma norepinephrine(NE) concentrations increased from 528±121 to 4138±912 pg/ml in controls and from 719±186 to 6958±1439 in naloxone-treated fetuses(NS). In contrast, a 27-fold increase in plasma E levels were noted following EOP blockade (254±58 to 6944±847 pg/ml) compared to a 10-fold increase in the controls(143±45 to 1391±290 pg/ml;p<.05). Thus, Nal potentiates the plasma E response to asphyxia. It is likely that EOP act as modulators of the sympathoadrenal response to severe stress in the fetus.

COCAINE AND PREGNANCY: MATERNAL AND INFANT OUTCOME.

387 Susan Livesay, Saundra Ehrlich, Loretta P. Finnegan. Jefferson Medical College of Thomas Jefferson University, Department of Pediatrics, Phila., PA.

The number of infants born to women who abuse cocaine is rapidly increasing. Subjects of this study, conducted within a drug treatment program providing pre and postnatal services to drug dependent women(DDW), included 237 pregnant women: 91 cocaine using DDW, 83 non-cocaine using DDW, and 63 non-DDW. The groups were similar for maternal age, socioeconomic status, nicotine use and parity, but differed in race. Abruptio placentae occurred in 8% of the cocaine DDW, 4% of the non-cocaine DDW and in 2% of the non-DDW. Spontaneous abortions, emergency C-sections and meconium staining occurred more often in the cocaine DDW than in either of the other 2 groups. Birth weight and length, head circumference, gestational age, and 1 min. Apgar scores were significantly lower in the infants of cocaine DDW. No differences existed in the occurrence of congenital anomalities and intracranial hemorrhage. There were more premature deliveries in the cocaine(21%) than in the non-cocaine(11%) and comparison(4%) groups. Mean neonatal abstinence scores, which incorporated 21 physiological and behavioral parameters to quantify symptoms, were lower for the cocaine exposed infants. Differences were significant with respect to cry, disturbed tremors, increased muscle tone, excoriations, fever, mottling, and loose stools. The results of this study suggest that: 1)cocaine use in pregnancy adversely effects maternal and infant outcome, 2)exposure to cocaine in-utero does not appear to increase the incidence of neonatal abstinence symptomatology.

ETHICAL CONSIDERATIONS IN PHARMACOKINETIC STUDIES IN NEONATES

388 David Long, Gideon Koren and Andrew G James. (Spon. by Stephen P. Spielberg). Divisions of Clinical Pharmacology and Neonatology, The Hospital For Sick Children, Toronto.

Parents, investigators and ethical committess must bear the responsibility for ensuring that the potential risks of research in the neonatal age group are acceptable and that the study will yield useful information. Pharmacokinetic studies require that multiple blood samples be taken. Because of potential hypovolemia and anemia in neonates, especially if pre term, it is essential that the least invasive study designs be used. This study aimed to determine the least number of samples that are required to obtain accurate pharmacokinetic parameters and dosing schedules by the analysis of 2 pharmacokinetic studies.

Neonates treated with ceftazidime or netilmicin who had had at least 6 samples taken after the first dose or during steady state were studied.12 concentration time curves from 10 infants on ceftazidime and 20 from 15 infants on netilmicin were used. Half life (T1/2), systemic clearance (Cl) and Volume of distribution (Vd) were calculated using all the available points and then recalculated using 2 points (the post dose and last), 3 points (first,last and mid time point), and 4 points.

Significant differences were found between results using 2 points and results using all the points for Cl and Vd for both drugs. When 3 points were used only Vd for netilmicin was different, and no differences were apparent when 4 points were used.

Using parameters obtained from 2 points, dosage would be underestimated by a mean of 15% (range 35% underdosage to 24% overdosage) for ceftazidime and by a mean of 11% for netilmicin (range 31% under to 14% overdosage). The corresponding figures for dosage based on 3 points were a mean underdosing of 1% (range 10% under to 14% overdosing) for ceftazidime and a mean underdosing of 5% for netilmicin (range 24% under to 7% overdosing). We conclude that 3 samples taken between doses may be all that are required for the estimation of pharmacokinetic parameters sufficiently accurate for practical purposes in neonates.

DISEASE SEVERITY AS A FACTOR IN ELIMINATION OF TOBRAMYCIN (TOBRA) IN PATIENTS WITH CYSTIC FIBROSIS (CF).

●389 Noni E. MacDonald, Robert F. Morris, and Robert G. Peterson, Children's Hospital of Eastern Ontario, Department of Pediatrics, Ottawa, Ontario Canada.

To obtain therapeutic "peak" and "trough" concentrations of tobra, many CF patients require ↑ dose/kg and ↑ frequency of drug administration. The basis for this is unclear. Tobra clearances after a single 60 mg/m^2 IV infusion were studied in 11 stable CF patients with mild to very severe disease to investigate factors which might modify tobra kinetics. The mean age was 16.5 years±3.5; range 10-22, with a mean NIH score of 63±19; range 32-94. The mean % weight for height was 93.1±17.5; range 63.1-122. The lung disease was mild to severe; mean FVC 70.2±23.5% predicted;, range 36-99; mean FEV1 53.4±27.5% predicted; range 17-97. The data could best be described by a two compartment model for drug elimination. Dosing based upon body surface area minimized the effect of malnutrition on attainment of therapeutic levels (mean peak 7.6±1.4mg/l). The half life ($T_{\frac{1}{2}}$) range was 1.24-2.52 hr, the volume of distribution (VD) range was 0.102-0.401 l/kg, the plasma clearance (TPC) range was 43-110 ml/kg/hr and the mean % dose recovered in urine by 24 hours was 78.7±18.5. VD and TPC were ↑ in patients with lower FVC, FEV1 % predicted; those with more severe disease (p's <0.02, strong correlation coefficients). NIH score (contains FVC) also correlated inversely but less strongly (p's < 0.05). Creatinine and inulin clearances correlated only with $T_{\frac{1}{2}}$ and VD respectively. Age, nutrition, and PAH clearance did not correlate. Thus, all CF patients are not the same in terms of tobra kinetics. These varied with the disease severity. This suggests that the severity of disease, not just the presence of CF, is the major factor for altered tobra kinetics.

BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD), 3-METHYLCHOLANTHRENE (MC), AND BENZO(A)PYRENE (BP) TO MOLYBDATE STABILIZED HUMAN PLACENTAL Ah RECEPTOR.

●390 David K. Manchester, Stephen K. Gordon, Cheryl L. Golas, Eve A. Roberts, and Allan B. Okey, Departments of Pediatrics and Pharmacology, University of Colorado, Denver, and the Division of Clinical Pharmacology, Hospital for Sick Children, Toronto.

Induction of human cytochrome P_1-450 by environmental pollutants is variable and may affect toxicity of many xenobiotics. This response to chemical exposures is genetically regulated in humans, but the mechanisms are poorly understood. In animals, a specific protein, the Ah receptor, regulates P_1-450 induction by substrate binding and nuclear interactions analogous to those of steroid hormone receptors. Previous efforts to identify a similar protein in human tissues have produced eqivocal results. We now report that human placenta, an organ with P_1-450 remarkably sensitive to maternal environmental exposures, contains Ah receptor. In the presence of 10 to 20 mM sodium molybdate, we consistently detected protein sedimenting at 9S on sucrose density gradients that specifically bound TCDD, MC and BP in order of decreasing affinity. This binding was highly specific for known P_1-450 inducers and no competition by steroid hormones could be detected. Binding affinities (Kd) were lower in placental preparations (15 nM) than in material from rodents (1-3 nM). Mean Ah receptor level in 10 placentas was 106 ± 13 fmol/mg cytosol protein in the presence of molybdate, but significantly lower (34 ± 6 fmol/mg protein) in its absence ($p < 0.001$). These results demonstrate that human placenta contains high concentrations of Ah receptor and suggest that P_1-450 induction in humans is regulated by mechanisms similar to those established for laboratory animals.

α_1 AND α_2 MEDIATED RENAL VASOCONSTRICTION IN FETAL (F) AND ADULT (A) SHEEP: ONTOGENY OF POST-JUNCTIONAL α ADRENOCEPTORS.

●391 G. Paul Matherne, Kenneth T. Nakamura, Oliva J. McWeeny, Beth M. Alden, Jean E. Robillard. University of Iowa, Iowa City, IA.

It has been suggested by others that renal hemodynamic response to α adrenoceptor stimulation is greater in newborns than adults (Am J Physiol 226:796, 1974). To further characterize the development of α adrenoceptors, the renal vascular response to specific α_1 and α_2 adrenoceptor stimulation using Phenylephrine (Phe) (α_1) and Guanabenz (Gb) (α_2) was determined in chronically catheterized F (132-140 days gestation; term 145 days) and A. Phe ($4.5x10^{-8}$M to $3.6x10^{-7}$M) or Gb ($6.2x\ 10^{-7}$M to $5x10^{-8}$M) was infused intrarenally and % changes in renal blood flow (%ΔRBF) were measured using a Doppler flow probe. α_2 mediated renal vasoconstriction was of smaller magnitude in F than A ($p<.001$ ANOVA); $ED_{50}F/ED_{50}A$ 5.3:1. However, α_1 mediated vasoconstriction was different only at the highest dose of Phe tested.

Gb α_2 Conc (M)	Fetus n=12 %ΔRBF	Adult n=8 %ΔRBF	Phe α_1 Conc (M)	Fetus n=8 %ΔRBF	Adult n=7 %ΔRBF
$6.2x10^{-7}$	-18±2	-30±3	$4.5x10^{-8}$	-18±6	-16±2
$1.25x10^{-7}$	-26±3*	-43±3	$9x10^{-8}$	-30±8	-26±4
$2.5x10^{-6}$	-33±3*	-50±4	$1.8x10^{-7}$	-41±9	-57±10
$5x10^{-6}$	-41±3*	-65±4	$3.6x10^{-7}$	-62±8*	-99±1

(*p<0.01, F vs. A, Newman-Keuls) In conclusion: 1) this study does not confirm previous observations of increased α-adrenoceptor activity during development, 2) post-synaptic α_2 adrenoceptors are functional in F, and 3) the F response to α_2 stimulation is less than A while α_1 response tends to be similar, suggesting a difference in the ontogeny of α_1 and α_2 adrenoceptors.