DEVELOPMENTAL PHARMACOLOGY

HEPATIC MICROSOMAL MIXED FUNCTION OXIDASE (HMMFO) AND THE HUMAN NEONATE: J.V.Aranda*, S.M.MacLeod*, K.W.Renton* and N.R.Eade (Intr. by M.E.Avery). McGill Univ., Dept. Pharmacol., and Montreal Children's Hosp. Research Inst., Montreal, Canada.

HMMFO catalyses the metabolism of drugs. Its activity has been measured in the human abortus but not in fetus and newborns of more advanced gestation. Determinations of the HMMFO components as shown below were performed on fresh liver biopsy or postmortem specimen obtained from 7 neonates (gestational age (GA) = 28-41 wks, birth weights = 725-3560 gms) and from 4 adults for comparison. The results show lower activity in the newborn compared to the adults. Postconceptional age (GA + postnatal age) correlates significantly with specific activity of HMMFO components and substrate oxidative enzymes. The data demonstrate a subcellular basis for deficient drug oxidative capability in the human newborn. Drugs requiring hepatic biotransformation for excretion (e.g. barbiturates) should be cautiously used in this age group.

	NEONATES (Range of Values)	ADULTS
Postnatal age	9 hrs-5 wks (7)	20-60 years (4)
Protein (mg/g liver)	18.8-25.5 (4)	not measured
NADPH oxidase*	0.97-3.5 (6)	not measured
Cytochrome (cyt) P450**	0.000-0.095 (7)	1.38-2.31 (4)
cyt c reductase*	9.65-87.10 (7)	45.5-207.6 (4)
cyt P450 reductase*	not detectable (4)	2.6-2.7 (2)
Aniline p-hydroxylase*	0.000-0.330 (7)	0.07-0.95 (4)
Aminopyrine N-demethylase*	0.035-1.880 (7)	0.98-3.76 (4)

*nmoles/mg protein/min; **nmoles/mg protein

POSTNATAL AGE: A DETERMINANT IN THE RESPONSIVENESS OF HEPATIC MICROSOMAL MIXED FUNCTION OXIDASE (HMMFO) TO THYROXINE (T4) EFFECT. J.V.Aranda*, K.W.Renton* and N.R.Eade* (Intr. by M.E.Avery). McGill Univ., Depts. of Pharmacol. and Ped., and Montreal Children's Hosp. Research Inst., Montreal, Canada.

Drug oxidative enzymes are refractory to induction in fetal rats 1 week (wk) prior to term but are readily inducible thereafter, indicating that age influences responsiveness of HMMFO to induction. To test whether postnatal age exerts quantitative and qualitative (induction or inhibition) effects in the response of HMMFO to drugs, T4, known to induce enzyme maturation, was given in equivalent doses of 1 mg/kg/day (d) x 3 d to male rats of varying ages (birth to 10 wks) followed by measurements of the component enzymes of HMMFO and substrate oxidations. Untreated rats of corresponding ages served as controls. The results show varying responses of HMMFO to T4 as a function of age. T4 decreased aminopyrine N-demethylase activity at 1-3 wks, had no effect at 4 wks, and induced at 5-10 wks. Reverse effects were noted with aniline p-hydroxylase, where induction was noted from 3 d to 4 wks followed by inhibition at 5-10 wks. Induction of NADPH oxidase was noted only at ages 3 d and 4 wks. NADPH cytochrome c reductase was highly inducible at all ages except at age 3 wks. Cytochrome P-450 was inhibited at all ages. The data show that the enzyme titres achieved in response to T4 is dependent on age. Where induction is desirable (e.g. of HMMFO, of lung surfactant, of glucuronyl transferase, etc.) the effectiveness of induction may depend on the age at which the inducer is administered.

EFFECTS OF MATERNALLY ADMINISTERED CORTISONE ON CYCLIC AMP AND PHOSPHOLIPIDS IN FETAL RABBIT LUNGS. Cynthia T. Barrett, Alex Sevanian, Norman Lavin and Solomon A. Kaplan, UCLA Sch. of Med., Dept. of Ped., Los Angeles.

Maternally administered cortisone (C) has not been reported to produce premature maturation of fetal rabbit lungs although this effect has been shown when C is injected directly into the fetus. We injected hydrocortisone (0.65 mg/kg) or saline subcutaneously (s.c.) t.i.d. into pregnant rabbits on days 24-26 of gestation. On day 26, under barbiturate anesthesia, we performed a laparotomy (sterile) and through the intact uterus injected ^{14}C CDP choline and ^{3}H methionine s.c. into the fetuses. On day 27 we killed the does and removed the fetuses. The 2 fetal groups were similar in body weight and length. We measured cyclic AMP (cAMP), total lipids, phospholipids (PL) and labeled phosphatidyl choline (PC) in the lungs. Components of PL were identical in the 2 groups.

	N	Mean cAMP pmoles/mg protein	Mean labeled PC (cpm/mg PC) ^{14}C	^{3}H
Control	4	0.295	7,760	4,868
Cortisone	4	0.517	11,708	7,680
p value		< 0.025	< 0.01	< 0.025

Preliminary evidence indicates that cAMP phosphodiesterase activity is inhibited in the C treated fetuses. We conclude that increased cAMP concentration is correlated with increased production of pulmonary surfactant and its early maturation following C administration.

A MICROTITER GAS CHROMATOGRAPHIC ASSAY FOR STUDY OF THEOPHYLLINE PHARMACOKINETICS. William J. Davis and Charles E. Pippinger (introduced by Robert B. Mellins). College of Physicians and Surgeons, Columbia University, Babies Hospital, Depts. of Pediatrics and Neurology, New York City.

Therapy of childhood asthma with theophyllines has been controversial and less than optimal because of a variable dose response relationship and unpredictable toxicity. Theophylline plasma concentration appears to correlate directly with pharmacologic effect and toxicity. The standard spectrophotometric (SP) method for theophylline is time consuming, requires large volumes of blood and is inaccurate in the presence of caffeine and other xanthines. An accurate gas chromatographic (GC) assay was developed and compared with the SP method. The GC response was linear from 0.5 to 100 μg/ml of plasma. Recovery of theophylline was 95%.

Ten children receiving theophylline preparations by oral and intravenous routes were studied. Peak plasma theophylline levels with the SP method ranged from 7.6 to 30.1 μg/ml, mean 18.2 ± 7.6; with the GC method the range was 4.8 to 18.4 μg/ml, mean 11.2 ± 4.6. Caffeine and other xanthine compounds did not interfere with the GC determinations. Assuming a two compartment open system model and first order kinetics, plasma half time ($t_{\frac{1}{2}}$) and elimination constants were calculated individually to determine a dose which would insure maximum therapeutic response and avoid toxic symptoms.

This rapid, accurate, specific, microtiter gas chromatographic assay has direct application to patient care.

NEONATAL MEPIVICAINE (CARBOCAINE^{R}) POISONING by W. Edwin Dodson, Richard Hillman, Laura S. Hillman, and Cheryl Alt. Washington Univ. Sch. of Med., St. Louis Children's Hospital, Dept. of Ped., St. Louis. Intr. by Philip R. Dodge.

A 23-year-old primigravida received 300 mg of mepivicaine via paracervical (100 mg) and pudendal (200 mg) injections, 60 min. and 30 min., respectively, prior to delivery of a term 3.1 kg infant. At delivery the baby was apneic and flaccid with a heart rate of 40. There were needle marks over the right parietal region. Despite resuscitation, placement of chest tubes for pneumothoraces, exchange transfusion and ventilatory support, the infant died of cardiac arrest associated with status epilepticus at 23 hours. Autopsy showed moderate hyaline membrane formation and intrapulmonary hemorrhage. Serum levels (μg/ml) by GLC were 16 at 7 hours, 15.4 at 11 hr (pre-exchange), 11.6 (post exchange), 9.8 at death, with a CSF level of 13 at 10 hr. GLC of fluid from scalp subcutaneous tissue at the site of needle marks showed a high concentration of mepivicaine. Post mortem tissue levels (μg/g wet weight) by GC-mass spectrometry using a multiple ion detector method with lidocaine internal standard were cortex 80.9, midbrain 77.1, pons 83.5, medulla 60.9, spinal cord 78.0, cerebellum 78.4, liver 87.8, kidney 58.6, fat 14.9, muscle 10.9. This case documents a fatal complication of the use of local anesthetics during labor. It demonstrates that mepivicaine may be concentrated in the neonatal CNS. The high CNS levels with lower serum levels suggest that exchange transfusion, if it is to be helpful, must be performed as soon as possible after delivery.

POSTNATAL DEVELOPMENT OF SYMPATHETIC INNERVATION OF HUMAN MYOCARDIUM. Scott L. Faulkner, Robert C. Boerth, and Thomas P. Graham. Vanderbilt University Hospitals, Division of Pediatric Cardiology, Nashville, Tennessee 37232

Whereas much information has accumulated on myocardial adrenergic mechanisms in adult man, little is known about these mechanisms in the newborn child. The effects of norepinephrine (NE), isoproterenol (ISO), cocaine ($C, 3x10^{-6}M$) and propranolol ($P, 1x10^{-6}M$) on contractile function were examined in isometrically contracting right atrial strips of 7 children age 5 months to 9 years, as well as in 4 papillary muscles and 3 atrial strips obtained at autopsy from 6 premature (estimated gestational age 18-34 weeks) and 1 full term infant. Dose-response curves to ISO in both groups were linear, parallel, and statistically identical. NE dose-response curves in both groups were also identical and shifted to the right of the ISO curves. P shifted the NE dose-response curve to the right in both groups to the same degree. Whereas C shifted the NE dose-response curve to the left in children, no shift was found in the newborn indicating that sympathetic innervation of the myocardium appears to be incomplete or functionally immature at birth in man. β-adrenergic receptors on the other hand are equally developed in the markedly premature infant and the older child and the myocardium may be expected to respond to catecholamines and β-adrenergic blockade in a similar manner in the two groups.