

**353** VALPROIC ACID (VPA): STEADY-STATE PHARMACOKINETICS IN PEDIATRIC PATIENTS WITH SEIZURES. N. Otten, K. Hall, J. Irvine-Meek, M. Verma, M. Leroux, D. Budnik, S. Seshia (Spon. by J.C. Haworth), Depts of Pharmacy, Pediatrics and Clinical Chemistry, Health Sciences Centre and University of Manitoba, Winnipeg, Manitoba, Canada

In view of the paucity of steady-state VPA pharmacokinetic data in children, we present the results from a study of 30 patients on this drug (doses of 15-46 mg/kg/day):

| Half-life<br>$t_{1/2}$ (hours) | Elimination Rate<br>Ke (hr. <sup>-1</sup> ) | Clearance (Cl)<br>ml/min/kg ml/min/m <sup>2</sup> | Vol. Distribution<br>Vd (l/kg) |
|--------------------------------|---|---|--------------------------------|
| 8.3 ± 2.6                      | 0.09 ± 0.03                                 | 0.31 ± 0.13                                       | 7.8 ± 3.04                     |
|                                |   | 0.20 ± 0.06                                       |                                |

Cl and Vd were higher in those receiving phenytoin and/or phenobarbital; the lowest Cl were found in 4 patients on methsuximide. Cl was inversely related to age and  $t_{1/2}$  was age and sex dependent:

|                  | Age (yrs.)        |                   | p     | Sex          |                | p     |
|------------------|-------------------|-------------------|-------|--------------|----------------|-------|
|                  | 0.1 - 9           | 10 - 20           |       | Male<br>n=16 | Female<br>n=14 |       |
| Cl (ml/min/kg)   | .36 ± .14<br>n=19 | .22 ± .08<br>n=11 | <0.01 | 0.34 ± 0.11  | 0.27 ± 0.15    | NS    |
| $t_{1/2}$ (hrs.) | 7.4 ± 2.1         | 9.9 ± 2.8         | <0.02 | 7.5 ± 2.0    | 9.4 ± 2.8      | <0.05 |

Peak and trough concentration ranges were 45 - 127 µg/ml and 13 - 101 µg/ml respectively; the variability in these concentrations emphasizes the need for specifying time of sampling in therapeutic monitoring. Our study also draws attention to (1) dependence of  $t_{1/2}$  on age and sex and (2) effect of other anticonvulsants and age on Cl of VPA. These data are of therapeutic import. This study was sponsored by White Cross Guild, MMSFI, and CHRF.

**354** EFFECT OF INTRAUTERINE EXPOSURE TO NARCOTICS ON CORD BLOOD CONCENTRATIONS OF PROLACTIN (PRL), CORTISOL (C), AND THYROXINE (T<sub>4</sub>) IN PRETERM INFANTS. Aruna Parekh, Trishit K. Mukherjee, Ramesh Jhaveri, Warren Rosenfeld and Leonard Glass. SUNY, Downstate Med. Ctr., The Long Island College Hosp. and the Jewish Hosp. and Med. Ctr. of Bklyn., Depts. of Ped. and Obs., Bklyn., NY.

PRL, C and T<sub>4</sub> enhance fetal lung maturation, and decreased cord blood levels of these hormones have been found in infants with RDS. Use of narcotics during pregnancy may both decrease the incidence of RDS and affect the metabolism of these hormones.

Cord blood concentrations were measured in 33 infants with a G.A. of 30 to 36 weeks. Ten were exposed to either heroin, methadone, or both and two of these developed RDS. Of the 23 non-narcotic exposed infants, 8 developed RDS and 15 did not.

The following results (median and range) were obtained:

|              | Prolactin (ng/ml) | T <sub>4</sub> (ug/dl) | Cortisol (ug/dl) |
|--------------|-------------------|------------------------|------------------|
| RDS          | 123.5(56.6-192.0) | 8.2(5.9-16.8)          | 18.0(10.6-24.7)  |
| No RDS       | 159.6(54.3-715.4) | 9.9(5.6-16.2)          | 28.6(1.6-93.3)   |
| Drug exposed | 179.6(55.1-323.3) | 9.5(5.1-21.3)          | 17.7(6.8-31.3)   |

The differences in PRL concentrations between the narcotic exposed and RDS groups were of borderline statistical significance (p=0.08), while levels of C were significantly higher in the no RDS than in the RDS or narcotic exposed groups (p<0.01). None of the other inter-group differences was statistically significant.

Intrauterine exposure to narcotics may play a modifying role in the synthesis of pulmonary surfactants.

**355** RECOMMENDED AMIKACIN DOSES IN NEWBORNS OFTEN PRODUCE EXCESSIVE SERUM LEVELS. Joseph Phillips; Celia Satterwhite; Meyer Dworsky; and George Cassidy.

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Emergence of a multiply drug resistant Enterobacter cloacae during a 7 week period in 1980 resulted in serious systemic disease in 4 infants and a high colonization rate in other infants in a newborn intensive care unit. Amikacin was employed as the aminoglycoside of choice in the initial treatment of suspected sepsis until the organism disappeared from the unit. Peak and trough serum amikacin levels were available in 18 infants. Recommended doses (7.5-10mg/kg loading; 15mg/kg bid IV) were given to 5 infants < 1000gm (range 590-980gm) and to 13 larger babies (range 1020-3300gm). Duration of therapy was similar in both groups prior to determination of antibiotic concentrations and averaged 3.2 ± 2.1 doses (x ± SD). Serum amikacin levels were measured using a Bacillus globii bioassay method with an accuracy of ± 1 µg/ml. Though levels 11.5 hours after a dose were 16.6 ± 11.9 µg/ml in infants < 1000gm and 6.5 ± 4.3 µg/ml in the larger infants (p < .02). Peak levels 1 hour post-infusion exceeded 40 µg/ml in 3 of 5 < 1000gm babies and 4 of 12 > 1000gm infants (p = NS). These data show that surprisingly excessive blood levels of amikacin are likely in infants < 1000gm and may also occur in larger infants using currently recommended dosage schedules (J. Pediatr. 91:358, 1977). These unexpected findings emphasize the need to monitor drug levels and individualize therapy in very low birthweight infants.

**356** PERSISTENT INDUCTION OF A CYTOCHROME P450 DEPENDENT MICROSOMAL ENZYME, ESTROGEN - 2-HYDROXYLASE, IN BRAIN AND LIVER, BY PRENATALLY ADMINISTERED PHENOBARBITAL. Merrily Poth, & Andrew Hoffman, Dept. of Pediatrics, Pediatric Endocrinology, USUHS, and NIMH, Bethesda, Maryland.

A major pathway of estrogen metabolism is 2-hydroxylation, catalyzed by a cytochrome P450 dependent microsomal enzyme. In the periphery the resultant metabolic product catechol-estrogen (CE), is rapidly inactivated. In brain however the locally produced CE has several specific effects, having its own specific receptors, competing for dopamine receptors in the pituitary and inhibiting both synthesis and metabolism of catecholamine neurotransmitters. In the immature male rat and in the female, but not in the mature male, the liver but not the brain enzyme is inducible by phenobarbital.

We injected pregnant female rats with phenobarbital on days 18 and 19 of gestation. We then measured estrogen 2-hydroxylase activity in the brain and liver of offspring on 1 through 21 days. Liver enzyme showed a biphasic response to this prenatal treatment with a 80% decrease in enzyme specific activity on days 1 & 2, and a 100% increase in enzyme activity persisting from days 5 through 21. Brain enzyme levels were significantly increased (↑50%) by this treatment from day 7 through day 21. This prolonged induction of a liver microsomal enzyme differs from that seen in young animals where enzyme activity returns to normal by one week after treatment. This is one of the first reports of a successful induction of brain microsomal cytochrome P450 enzyme.

**357** DISPOSITION OF <sup>14</sup>C-PHENYTOIN IN THE PREGNANT AND NON-PREGNANT BABOON. Tonse N. K. Raju, Louette Paul, Frank Z. Beluhan, Michael A. Evans and Dharmapuri Vidyasagar, Departments of Pediatrics and Pharmacology, University of Illinois Medical Center, Chicago, IL 60612.

The maternal and fetal disposition of <sup>14</sup>C-phenytoin (DPH) was evaluated in the pregnant (125-160 days) and non-pregnant baboon. Five pregnant and four non-pregnant female baboons (12-17 kg) were pre-anesthetized with ketamine (7 mg/kg) and maintained under halothane during the first 5 hrs of study. <sup>14</sup>C-DPH was administered intravenously as a 5 mg/kg bolus dose and blood, urine and amniotic fluid samples were collected for 48 hours. Results from pharmacokinetic analysis were (mean and SEM).

|              | Half Life (hr) | Dist. Volume (l/kg) | Cl. (ml/hr/kg) |
|--------------|----------------|---------------------|----------------|
| Pregnant     | 22 (1.02)      | 1.79 (0.10)         | 57.2 (2.4)     |
| Non-Pregnant | 14.9 (.66)     | .99 (.05)           | 46.3 (3.1)     |

During the first 5 hrs a significant decrease was observed in the urine output from pregnant animals of the DPH diol and conjugated metabolites (HPPH). In amniotic fluid DPH and HPPH concentrations reached 50% of maternal serum concentration within 24 hrs following DPH administration. At 48 hrs the amniotic/serum ratio for HPPH rose to 0.85 while the DPH ratio remained at 0.50. No other DPH metabolites were observed in the amniotic fluid. It is concluded that during pregnancy DPH conjugation and diol formation are reduced while dist. vol. is increased. The decrease in DPH half-life during pregnancy appears to reflect the increase in dist. vol. rather than changes in clearance (metabolism).

**358** EFFECT OF GENTAMICIN ON NEUROMUSCULAR FUNCTION (NMF) OF A HYPERMAGNESEMIC NEONATE. Deborah K. Rasch and C. Joan Richardson. (Spon. by Ben H. Brouhard). University of Texas Medical Branch Hospitals, Department of Pediatrics, Galveston.

Treatment of maternal pre-eclampsia with MgSO<sub>4</sub> is reported to produce flaccidity, lethargy and hyporeflexia in their infants. Aminoglycosides can also affect NMF. Both agents interfere with release of acetylcholine, producing a defect in neuromuscular transmission. A term infant was born to a pre-eclamptic mother treated with 28 gm MgSO<sub>4</sub>. The baby had cord blood Mg<sup>++</sup> of 3.9 mg/dl and demonstrated neuromuscular compromise as measured by ulnar nerve stimulation studies and neurologic examination. Improvement occurred as serum Mg<sup>++</sup> level approached normal (1.5 ± 0.2 mg/dl). At 48 hrs. of age, septicemia was suspected and antibiotics (ampicillin 50 mg/kg IV q 12 hrs. and gentamicin 2.5 mg/kg IV q 12 hrs.) begun. Two hours after receiving the second dose of gentamicin, the infant had respiratory, followed by cardiac arrest. Resuscitation was successful and 24 hrs. later NMF was studied before and after a gentamicin dose. Increasing fatigability of NMF occurred at 1 and 2 hrs. after gentamicin. This case suggests that depressed NMF in a hypermagnesemic infant may be further compromised by aminoglycoside therapy.