415

DRUG DEPENDENCE IN PREGNANCY: INTRAPARTUM COURSE AND MANAGEMENT, Harris Silver, Ronald Wagner, Pawan Rattan, Mark Lorz-Vega and Loretta Finnegan, Jefferson Medical College of the Thomas Jefferson University, Philadelphia, PA.

It is known that drug dependent women (DDW) have an increased incidence of medical and obstetrical complications, but little information exists on the intrapartum course and management of these patients. Within the context of Family Center, a clinical and research program providing comprehensive pre- and postnatal services for DDW and their infants, a study was undertaken to determine if the DDW had normal patterns of labor and if standard intrapartum management is appropriate. The study population included 336 women who delivered between January 1982 and July 1984, of which 112 were DDW (72% receiving methadone maintenance). The comparison group of 224 non-drug dependent women was matched for gravity, parity and socioeconomic background. The incidence of premature delivery, abruptio placentae, breech presentation and intrauterine growth retardation were significantly greater in the DDW. The average duration of the first, second and third stages of labor compared well with the normal course of labor and matched the results of the comparison group. Labor abnormalities and cesarean sections were of no greater incidence, but there were more than twice as many forceps deliveries which coincides with the 40% increased use of epidural anesthesia. Analgesia and anesthesia were in excess of that which is given to the average patient. There were three stillbirths, one neonatal death, and one maternal death. Apgar scores and the incidence of fetal distress and meconium staining were identical in both groups. Postpartum complications were more common in the DDW, but most were secondary to the use of subclavian intravenous lines inserted due to the presence of sclerotic veins. These data suggest that high risk prenatal management and careful monitoring in the intra- and postpartum periods utilizing epidural anesthesia identifies and usually prevents untoward complications in DDW.

416

THE TOXICITY OF ACETAMINOPHEN ANALOGUES IN LYMPHOCYTE CULTURE. Camal Soliman, Marthe Delpé-Scott, and Robert G. Peterson. University of Ottawa, Department of Pharmacology and Pediatrics, Ottawa, Ontario, Canada.

Acetaminophen (A4AP) is known to be activated by oxidative metabolism to a reactive iminoquinone. Two structural analogues, N-Acetyl-3-AminoPhenol (A3AP) and N-Acetyl-2-AminoPhenol (A2AP) have been studied as to their oxidation. A2AP is more reactive than A4AP whereas A3AP is not oxidizable to an iminoquinone using an electrochemical cell. Using the *in vitro* human lymphocyte/mouse hepatic microsome method which demonstrated toxicity of A4AP we have shown that A2AP is a more potent cytotoxic agent than A4AP and that A3AP is devoid of toxicity (Table). This is consistent with the observation that A3AP is not hepatotoxic in animals but contradicts the observation that A2AP was also not hepatotoxic. Previous arguments as to the necessity for N-hydroxylation to activate A4AP to a reactive species are not substantiated by these observations. A2AP, not hydroxylated due to steric constraints, is readily oxidized and is very cytotoxic. Its apparent lack of toxicity in animals was likely an artifact of its rapid clearance *in vivo*. A3AP, the non-toxic analogue *in vitro* and *in vivo*, represents an interesting alternative to A4AP as a new therapeutic agent.

		Percent Cell Death				
mcg/ml in incubate	→	0	100	500	1000	1500
A4AP (n=28)	-	-	2	5	16	36
A3AP (n=28)	-	-	1	2	2	4
A2AP (n=28)	-	-	3	29	58	80
Control (n=30)	1	-	-	-	-	-

417

PHARMACOGENETIC PREDISPOSITION TO PHENYTOIN-INDUCED BIRTH DEFECTS. S.Strickler, L.Dansky, E.Andermann, S. Spielberg, Hosp. Sick Children, Div. Clin. Pharmacol. Toronto; Montreal Neurol. Inst., Dept. Neurogenetics, Montreal.

The role of phenytoin (DPH) in causing birth defects is uncertain. Only a minority of fetuses exposed to DPH have malformations. Arene oxide metabolites (AOM) of DPH may be involved in fetal toxicity. We found genetic differences in detoxification of AOM in patients with adverse reactions to DPH. Therefore, we have explored the contribution of detoxification defects to DPH-induced birth defects. 29 children from 18 families exposed to DPH during gestation and their parents were studied using an *in vitro* assay in which lymphocyte capacity to detoxify AOM is assessed. Analyses were performed blind to the identity and clinical findings of the subjects. A positive(+) test showed a significant increase in cell death in the presence of 62.5uM DPH and a metabolite-generating system. Following completion of *in vitro* studies, physical findings were analyzed for all subjects. There was an increase in major malformations in + subjects:

	POSITIVE(n=16)	NEGATIVE(n=13)
CONGENITAL HEART DISEASE	5	0
CLEFT LIP/PALATE	3	0
MICROCEPHALY	13	1

Scoring minor and major anomalies, there was a significant increase in number and severity of malformations in + patients. For each + patient, one or both parents were +. An inherited deficiency in detoxification of AOM of DPH may modify the outcome of *in utero* exposure to the drug.

418

PEDIATRIC PHARMACOKINETICS OF IMIPENEM. M.C. Thirumoorathi, Barbara A. Tereshinski, Denise M. Kobos and Adnan S. Dajani. Wayne State Univ. Sch. Med., Children's Hospital of MI., Dept. Peds., Detroit.

Only limited data are available on the pharmacokinetics of imipenem, a new carbapenem antibiotic, in children. We treated 14 children (age 8 mo to 10 yrs) who had non-CNS infections with imipenem-cilastatin. Children <3yrs of age were given 25mg/kg/dose of imipenem as a 60 min. IV infusion every 6h. Older children were given 15 mg/kg/dose. Serial blood samples were obtained after multiple doses (>10) in all children. The plasma concentrations of imipenem (assayed microbiologically), and the calculated pharmacokinetic parameters are as follows:

Dose	N	Predose	Plasma imipenem levels (mg/L)			
			Peak	1h	4h	5h
25 mg/kg	9	0.92±0.39	61.4±13.2	19.4±3.8	1.59±0.64	0.76±0.43
15 mg/kg	5	0.55±0.14	36.5±5.2	10.4±1.5	0.78±0.33	0.26±0.26

Dose	N	AUC (mg.h/L)	Vd (ml/kg)	Clp (ml/min/kg)	T _{1/2} (h)
25 mg/kg	9	95.3±17.5	295±45	4.5±0.8	0.77±0.10
15 mg/kg	5	54.9±8.5	313±54	4.6±0.7	0.78±0.11

p = 0.0004 0.49 0.70 0.82

In 4 patients (2 in each dose group) the pharmacokinetics of imipenem after the initial dose and after multiple doses were compared. There were no statistically significant differences.

The pharmacokinetics of imipenem are similar in younger children (8 mo to 3 yrs) and older (3-12 yrs) children. A dose of 15 mg/kg/dose q6h would provide satisfactory plasma levels without drug accumulation in both age groups.

419

FAMILIAL PYRIMIDINEMIA AND PYRIMIDINURIA, A NEW PHARMACOGENETIC DISORDER? M. Tuchman, J.S. Stoeckeler, D.T. Kiang, R.F. O'Dea, M.L. Ramnaraine and B.L. Mirkin, Univ. of Minnesota, Dept. of Pediatrics and Div. of Clin. Pharmacol., Minneapolis, Minnesota.

Two siblings were found to have elevated plasma concentrations and increased urinary excretion of uracil (U) and thymine (T) (as high as 50 times normal for U and 100 times normal for T, when compared to 17 healthy adult controls). The female sibling developed severe neurotoxicity after chemotherapy with 5-fluorouracil (5-FU) for breast cancer. Both had normal serum and urinary uric acid concentrations and also normal urinary orotic acid levels. Thymidine kinase activity in the female's WBC was normal 17.30 pmoles/mg protein/min (controls 19.37±7.02). Three other members of the family (mother and two other siblings) had normal plasma and urine levels of U and T.

	Urine (µg/mg creatinine)		Plasma (µg/ml)	
	Uracil (N)	Thymine (N)	Uracil (N)	Thymine (N)
Sister	99±35 (10)	126±27 (10)	0.7±0.1 (6)	1.5±0.5 (6)
Brother	110±39 (3)	92±26 (3)	0.9 (1)	2.4 (1)
Controls	2.1±0.8 (17)	<0.05 (17)	0-0.05 (3/17)	<0.01 (17)

This metabolic aberration can be explained by the decreased degradation of U, T and 5-FU in the liver. Degradation of pyrimidine bases could not be demonstrated in normal fibroblasts. The activity of dihydropyrimidine dehydrogenase was assayed in rat liver. 5-FU was found to be a substrate for this enzyme *in vitro*. We postulate that the two siblings have a defect in hepatic dihydropyrimidine dehydrogenase causing decreased degradation and enhancement of 5-FU toxicity in one sibling.

420

THE COURSE OF HYPERBILIRUBINEMIA IN THE VERY LOW BIRTHWEIGHT INFANT TREATED WITH PHENOBARBITAL. Julio Valdivieso, Mujahid Anwar, I. Mark Hiatt, Thomas Hegyi, Div. of Neonatology, Dept. of Pediatrics, UMDNJ-Rutgers Medical School, St. Peter's Medical Center, New Brunswick, N.J.

We examined the effect of early phenobarbital therapy on the course of jaundice in 58 infants below 1500g. The study group of 28 infants (BW 1149±251g, GA 29.5±2.7wks), was treated with a phenobarbital loading dose of 20mg/kg/day at 4.2±3.6 hrs of age, followed by a maintenance dose of 5mg/kg/day for one week. Thirty infants served as controls. Seventeen study and 20 control infants suffered from intraventricular hemorrhage.

The results of the comparison showed that treated infants had lower peak serum bilirubin concentrations (7.9±1.7 vs 8.6±2.2mg/dl), reached peak SBC levels earlier (92.5±50.7 vs 138.0±101.1 hrs) and spent less time on phototherapy (5.5±2.9 vs 7.5±3.8 days). In the study group, although peak SBC was similar to that of no IVH infants, the IVH subgroup reached peak SBC later (112.8±53.0 vs 61.2±25.6 hrs) and spent more time on phototherapy (6.9±2.3 vs 3.2±2.4 days). Control IVH infants showed similar results with an age at peak of 150.0±100.3 vs 114.1±101.4 hrs and a duration of phototherapy of 8.8±3.7 vs 4.8±2.5 days when compared to control infants without IVH.

In this group of infants P was effective in reducing the severity of hyperbilirubinemia as indicated by the decreased need for therapy. In addition, the presence of IVH contributed to the hyperbilirubinemia in both treated and control infants.