397 VARIATION AND SIGNIFICANCE OF ELEVATED CORD SERUM BROMIDE CONCENTRATION (CSBC). Marvin E. Miller and Janice M. Cosgriff. (Spon. by William Maniscalco) University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital, Department of Pediatrics, Rochester, N.Y.

At least 4 cases of neonatal bromism secondary to maternal ingestion or exposure to bromide-containing compounds during pregnancy have been reported. The cardinal features in these babies were weakness and hypotonia. The maternal exposure in 3 cases was from drugs and in one case from presumed occupational exposure to bromide salts in the photographic film manufacturing industry. To determine the variation in CSBC and whether unsuspected neonatal bromism might be responsible for unexplained neonatal problems, we measured the CSBC in 196 consecutive babies born at Strong Memorial Hospital, Rochester, N.Y., during January 1984, using a sensitive HPLC method. The CSBC ranged from 3.4 - 17.0 mg/l with a mean ($\pm$ 1 SD) of 7.4 mg/l $\pm$ 2.1. There was no apparent increased frequency of neonatal complications in babies with higher CSBC. Most noteworthy was that the highest CSBC (17.0 mg/l) was in a baby whose mother was a professional photographer. This study suggests that there is variation in CSBC and that occupational exposure to bromides from use or processing of photographic film may cause increased CSBC.

398 AN IMPROVED APPROACH TO NEONATAL THERAPEUTICS. Gail Murphy, Leonard E. Weisman, Carl C. Peck, Fitzsimons Army Medical Center, Department of Pediatrics, Aurora, CO. (Sponsored by Frederick Battaglia)

It is difficult to achieve a therapeutic range rapidly because of individual variations in clearance (Cl) and distribution volume (Vd). Sheiner et al prospectively validated a Bayesian approach to individualizing Cl and Vd in adults. We have studied the usefulness of this microcomputer approach in the neonate. The charts of 11 newborns treated with theophylline were retrospectively reviewed. Average values for Cl and Vd taken from the literature were assumed for each infant. Initial estimates were revised with the first serum level. Individualized Cl and Vd were used to predict the second theophylline level. Predictions were not significantly different from measured levels. We found that Bayesian theophylline dosing program could estimate an individual neonate's theophylline Cl and Vd with as few as one serum level with acceptable accuracy.

Gentamicin dosing decisions were then studied prospectively. Serum levels were obtained immediately before the second dose. Published values for Cl and Vd were individualized using the trough level and the Bayesian program. Dose revisions were made using individual Cl and Vd. Followup levels were obtained in 72-96 hours. In 19 of 20 infants, followup levels were in the therapeutic range. Predictions were not significantly different from measured levels. We conclude that dosing schedules which are individualized based on 1 serum level and the Bayesian microcomputer program make achieving therapeutic levels quick and accurate.

† **399** FETAL RITODRINE EXPOSURE AND NEONATAL OUTCOME. M.N. Musci Jr., S. Abbasi, C. Otis. (Spon: Lois Johnson). Univ. of Pennsylvania, School of Medicine, Dept. of Peds. and Ob/Gyn., Pennsylvania Hosp., Philadelphia, Pa.

Ritodrine Hydrochloride (R) experience was reviewed after the first two years of regular use (7/81-6/83). Of the 202 women treated, 159 (78%) carried the pregnancy to 35 weeks or greater. Neonatal outcomes including birthweight (BW), gestational age (GA), Apgar scores, hypoglycemia, hyperbilirubinemia, RDS, IUGR and mortality were correlated with (1) duration of exposure, (2) onset of exposure and (3) interval from cessation of exposure to delivery. Infants exposed to R for $\geq$6 wks ($\bar{X}$=11.4) were significantly heavier (3109g vs 2884g, $p<.01$) than infants exposed for <6 wks ($\bar{X}$=3.6). This could be accounted for by a significant difference in the corresponding GA at birth (38.9 vs 37.4 wks, $p<.001$). Those infants exposed to R beginning at $\leq$ 30 wks $\bar{X}$=25.0 wks gestation) had a significantly greater ($p<.05$) need for phototherapy than did the infants with exposure beginning at >30 wks ($\bar{X}$=32.8 wks gestation). Neither duration of exposure or GA at birth were significant factors for hyperbilirubinemia. Early hypoglycemia was seen in 11/159 infants (7%). 10/11 of these infants (91%) were exposed to R until the day of delivery. This incidence differed significantly from that among infants whose exposure stopped at least 1 week prior to delivery. Apgar scores, RDS, IUGR and mortality were not significantly different. In conclusion, R therapy prolongs pregnancy and decreases prematurity rate. Hyperbilirubinemia is increased in infants exposed to R earlier in gestation regardless of GA at birth. Hypoglycemia is more frequent in infants exposed up until delivery date.

400 DOES DRUG ADDICTION DURING PREGNANCY ENHANCE DRUG BIOTRANSFORMATION BY THE PLACENTA? Enrique M. Ostrea Jr., James Balun, Wayne State U., Hutzel Hospital Department of Pediatrics, Detroit.

The placenta is not merely a passive barrier to drugs and foreign chemicals, but may participate in xenobiotic biotransformation, as well. It is not known whether chronic addiction during pregnancy enhances this placental function. We therefore studied placental homogenates from 5 normal control and 7 drug dependent mothers and compared their oxidoreductase and transferase activities (μmoles/mg protein/h). RESULTS: (1) Reductase activity (measured by neoprontosil reduction) was higher in the soluble than microsomal fractions, due mostly to catalysis by NADPH. No significant difference was seen in the reductase activity of control (0.72 + 0.06) vs addict (0.74 + 0.16) in the supernate. (2) Transferase activity (by bilirubin conjugation) was minimal in both soluble and microsomal fractions. No significant difference was noted in the microsomal transferase activity of control (0.11 $\pm$ 0.06) vs addict (0.12 $\pm$ 0.05) homogenates. (3) Mixed function oxidoreductase activity (by aniline p-hydroxylation) appeared higher in the soluble (0.64 + 0.24) than the microsomal (0.21 + 0.14) fractions but due solely to hemoglobin in the soluble fraction which nonenzymatically catalyses aniline hydroxylation (49.4 x 10^{-4}umoles/mg Hgb). No enzymatic oxidoreductase activity was noted in the control or addict homogenates. CONCLUSION: Little to no xenobiotic oxidoreductase and transferase activity was noted in both control and addict placental homogenates. Apparent activity was principally due to nonenzymatic catalysis of substrates by NADPH or Hgb. Thus, despite chronic exposure to drugs, the placenta of drug addicted mothers does not show any enhanced xenobiotic biotransformation activity and therefore offers no adaptive protection to the fetus.

401 ADVERSE EFFECTS OF MEPERIDINE (M), PROMETHAZINE (P) AND CHLORPROMAZINE (C) COMBINATION FOR SEDATION/ ANESTHESIA IN PEDIATRIC PATIENTS. Milap C. Nahata, Michael A. Clotz and Elizabeth A. Krogg, Ohio State University Colleges of Pharmacy and Medicine, Children's Hospital Department of Pediatrics, Columbus, Ohio.

M (25 mg/ml), P (6.5 mg/ml) and C (6.5 mg/ml) combination is widely used to produce sedation/anesthesia in pediatric patients. Although a dose of MPC, 0.1 ml/kg, is recommended for cardiac catheterization, no specific dosing guidelines and frequency of monitoring have been established for patients undergoing other procedures. The adverse effects of MPC were studied prospectively in 95 patients undergoing various procedures. MPC was given parenterally at a dose of 0.02-0.20 ml/kg. Vital signs, blood pressure, pulse rate and respiratory rate were monitored during 8 hr after the dose. Four patients developed severe respiratory depression. In these patients, the lowest respiratory rate ranged from 6 to 18 per min at 1 to 3 hr. The lowest pulse rate ranged from 92 to 102 per hr at 1 to 2 hr. One patient receiving MPC, 0.07 ml/kg, developed respiratory arrest within 30 min. One patient required naloxone and all recovered within 12 hr. About two-thirds of 95 patients were sedated for longer than 7 hr. These data suggest the need for frequent monitoring and specific dosing guidelines for MPC use in pediatric patients.

402 TOBRAMYCIN PHARMACOKINETICS IN IDENTICAL TWINS DURING NEWBORN PERIOD. Milap C. Nahata, Dwight A. Powell, Marcia A. Miller. The Ohio State University Colleges of Pharmacy and Medicine, Children's Hospital Department of Pediatrics, Section of Infectious Diseases, Columbus, Ohio.

Tobramycin is commonly used in newborn infants but little is known about its pharmacokinetics in identical twins. We studied six infants (gestational age 29-31 weeks; postnatal age 3-4 days; birth weight 1.0-1.3 kg) receiving tobramycin 2.5 mg/kg IV over 20 minutes every 12-18 hours. On third day of therapy, blood samples were collected at 0, 0.5, 1, 2, 4, 8, 12 and 18 hours after starting the infusion and analyzed by EMIT. Peak and trough serum concentrations of tobramycin ranged from 5.3-8.4 μg/ml and 1.2-2.0 μg/ml, respectively. Total clearance (cl_T) ranged from 0.74-1.19 ml/min/kg, distribution volume (V) from 0.74-0.94 L/kg, and elimination half-life ($t_{\frac{1}{2}}$) from 8.2-12.8 hours. Comparison of data between infants in three identical twin pairs showed that despite a similar infusion method: (a) the time to achieve peak serum concentration ranged from 0.5-2.0 hours; (b) the peak and trough concentrations varied from 0-50%; and (c) the cl_T, V and $t_{\frac{1}{2}}$ varied from 3-20%. These data indicate that peak and trough serum concentrations may be more variable than the kinetic parameters in identical twins. This information should be considered in therapeutic drug monitoring of tobramycin in identical twins during the newborn period.