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METHYLMERCURY EXCRETION: DEVELOPMENTAL CHANGES IN MOUSE AND MAN. Richard A. Doherty, Allen H. Gates and Timothy D. Landry, Depts. Pediatrics, Obstetrics

Radiation Biology/Biophysics; Univ. of Rochester, Rochester, N.Y. During winter 1971-72 massive poisoning occurred throughout rural Iraq due to ingestion of homemade bread prepared from seed wheat treated with a methylmercury(CH₃Hg) fungicide. Thousands of children and adults were poisoned and hundreds of deaths occurred (Science 81:230,1973). Prenatal and early postnatal exposure were documented (Ped. 54:5,1974; AJDC 130:1070,1976) and long term followup studies of exposed fetuses and infants are in progress. Using a mouse model to determine potentially significant variables relating to CH₃Hg toxicity in the developing mammal, we have observed that compared to adults, suckling mice excrete minimal amounts of their body burdens of mercury. Groups of young mice were exposed to a single non-toxic dose of CH₃²⁰³Hg (0.4 mg/Kg. per os) at 2,4,6, or 28 days of age. Whole body counts and urinary and fecal excretion were followed for each exposure group. From birth to 15 days, elimination half-times of mercury ranged from 2500 to 200 days. Between 16 and 18 days an abrupt increase to the adult elimination half-time of 8 days occurred. Decreases in whole body counts were accurately reflected in counts recovered in excreta. Studies are underway to determine whether a similar developmental change in excretion occurs in the exposed human infant. Since elimination half-time has been shown to be directly related to cumulative body burden as a function of duration of exposure, these observations are of importance in estimating exposure risks of human fetuses and infants.

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PERINATAL HYPERMAGNESEMIA: RELATION TO GESTATIONAL AGE AND BIRTH ASPHYXIA. Edward F. Donovan, Jean J. Steichen, Robert J. Strub, Reginald C. Tsang. U. of Cincinnati, Departments of Pediatrics & Obstetrics, Cincinnati.

Pre-eclamptic mothers (n=22) treated with MgSO₄ and their infants (32-44 wks gestation) were studied during labor and the first 3 days of postnatal life. Maternal serum Mg increased from 2.09±.09mg/dl (mean±SEM) prestudy to peak 5.54±.52 and 4.44±.41 at delivery. Neonatal Mg at 6-12 hrs of age (4.15±.20) was lower than placental vein Mg (4.79±.38), paired t, p<.05, and continued to fall postnatally (3.39±.15 at 24 hrs, 3.07±.15 at 48 hrs), but remained elevated (3.03±.18) at 72 hrs. Infant serum Mg at 48 and 72 hrs of age was higher in premature infants (Mg vs gestation, r=-.679, p<.01 and r=-.628, p<.05). Infants with birth asphyxia (1-min Apgar <6) had higher serum Mg at 48 hrs (3.60±.42 vs 2.86±.10, p<.05). Urinary Mg excretion was low, .094±.048 mg/day on day 1, but increased to 5.47±4.91 on day 3 (n=5, paired t, p<.07). Infant serum Mg at 24, 48 and 72 hrs was directly related to maternal Mg levels prestudy (r=-.679 - .792, p<.05) and at 24 and 48 hrs was directly related to the total dose of Mg given to the mother (r=-.737, .704, p<.01). Four infants judged to be hypotonic by an observer blind to Mg levels (arbitrary neurologic scale) had higher Mg levels at 24 and 72 hrs (p<.05). No relation of serum Mg with electrocardiograms was shown; PR was prolonged (>.12 sec) in 5 of 10 infants and prolonged QTc (>.4 sec) in 4 of 10. Thus, maternal Mg excess is associated with prolonged neonatal hypermagnesemia; premature and birth asphyxiated infants have greater intolerance to Mg excess.

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CENTRAL NERVOUS SYSTEM LEVELS OF CHLORAMPHENICOL IN PREMATURE INFANTS. Lisa M. Dunkle. (Intr. by A. E. McElfresh). St. Louis University School of Medicine, Cardinal Glennon Memorial Hospital for Children, Department of Pediatrics, St. Louis, Missouri.

Studies of neonatal meningitis have shown the need for antibiotic therapy that reliably reaches the central nervous system (CNS) in therapeutic levels. In four infants being treated for bacterial meningitis or ventriculitis, chloramphenicol levels were measured in serum on 21 occasions and in cerebrospinal fluid (CSF) or ventricular fluid on 21 occasions. Drug levels were determined by a colorimetric procedure which measures only the active form of the drug. Patients received chloramphenicol in doses of 25-35 mg/kg/day divided in two intravenous infusions. The peak level of chloramphenicol in serum was 36.3 ± 15.3 µg/ml (mean ± S.D.) and the trough level was 24.0 ± 11.8 µg/ml. CNS fluid levels had a mean of 22.2 ± 8.9 µg/ml. Thus, chloramphenicol entered the CNS in therapeutic levels, in 60-90 per cent of serum levels. CNS infection was sterilized within 4 days in two infants with normal CSF dynamics while ventricular fluid was sterile by 5 and 9 days in the infants with pre-existing hydrocephalus. All four infants had a good clinical response and none exhibited signs of chloramphenicol toxicity after 18-21 days of therapy.

With the documentation of adequate and safe therapeutic levels of chloramphenicol in the CNS in premature infants, it seems unnecessary to pursue more invasive techniques for the administration of aminoglycoside antibiotics.

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DIFFUSION OF METHYL MERCURY (mHg) IN BLOOD. Yigal Greener & Joseph A. Kochen, Albert Einstein Coll. Med., Montefiore Hosp. & Med. Ctr., Dept. Ped., The Bronx, NY.

The fetus is particularly susceptible to the toxic effects of mHg. Comparisons of mHg content of maternal and newborn blood have shown increased levels in the newborn. This has been attributed to facilitated transplacental diffusion because of high fetal hematocrit (Hct). This study shows the converse, that the diffusion of mHg diminishes progressively with increasing Hct. The diffusion of m²⁰³Hg across a Millipore membrane (.45µ) separating compartments A and B of a diffusion cell was studied. When both compartments contained saline or plasma alone, equilibration from A to B occurred in 5 hours. Introduction of human red blood cells (RBC) in saline (Hct 20%) in B, resulted in a 2-fold increase in diffusion of mHg when compared to saline alone. Increasing Hct resulted in a progressive decrease in diffusion. At Hct 80%, the increase in diffusion seen at Hct 20% was completely abolished. The presence of RBC in plasma (Hct 20%) in B, resulted in a 60% decrease in diffusion; with increasing Hct, diffusion was further reduced (r = -0.95, p < .001), until at Hct 80% it was < 5% of that in plasma alone. Direct addition of mHg to RBC in saline resulted in 98% RBC uptake. Increasing concentrations of plasma (at constant Hct) resulted in a progressive decrease in RBC uptake. In undiluted plasma at Hct 14%, RBC uptake of mHg was 35%. Plasma electrophoresis showed that much of mHg was associated with a high molecular weight lipoprotein fraction. Plasma components appear to be important in the distribution of mHg in blood and may be a factor in the relatively higher blood levels in the fetus.

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METHYL MERCURY TOXICITY IN THE CHICK EMBRYO. Y. Greener and J.A. Kochen, Albert Einstein Coll. Med., Montefiore Hosp. & Med. Ctr., Dept. Ped., The Bronx, NY.

Methyl mercury (mHg) can have a devastating effect on the integrity of the nervous system. Previous studies have shown that the fetus is at particular risk. The administration of m²⁰³Hg to the pregnant rat resulted in a substantially higher level in the brains of fetuses than in the dam (12.6 ± 2.6 (9) vs 3.0µg/gm dry wt.) (M ± SD). In the chick embryo, the LD-50 for mHg injected into the yolk sac on Day 5 was 50µg. Embryos dying within 24 hours showed increased total body mHg levels when compared to survivors (219 ± 67 vs 105 ± 41µg/gm). Absorption was dose-related, with a good correlation between mortality and body, blood and brain levels. Daily analysis of body mHg levels after injection on Day 5 showed continued mHg accumulation (0.88 ± 0.35µg/embryo/day). However, the rate of embryo growth exceeded the rate of mHg absorption, resulting in a progressive decrease in mHg concentration (from 94.5 ± 34.2µg/gm on Day 6 to 45.3 ± 13.4 on Day 9). Administration after Day 5 resulted in a significant reduction in levels of mHg in brain on Day 18 (from 11.4 ± 2.1µg/gm when given on Day 5 to 8.4 ± 2.3 when given on Day 9) and in mortality (from 64 to 33%). Since blood mHg levels remained unchanged, the increased brain levels and higher mortality early in embryogenesis may reflect facilitated transfer of mHg across a poorly developed blood-brain barrier. Later in development, the reduced mortality and lower brain mHg levels correspond to the formation of specialized inter-endothelial junctions and a more effective blood-brain barrier.

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RATIONAL DRUG THERAPY IN CHILDREN: CONSIDERATION OF THE EFFECTS OF DEVELOPMENTAL CHANGES OF DRUG CLEARANCE. Rolf Habersang (Spon. by Cheng Cho). Dept. Ped. Univ. Ka. Sch. Med., Kansas City, Kansas 66103

More than sixteen formulas have been devised to allow adjustment of average adult drug doses for infants and children. Clark's rules based on body weight or body surface extrapolation are used most commonly, but they do not take into account the developmental changes of the function of the eliminatory organs and/or of the relative body composition. These developmental changes result in corresponding changes of drug elimination and volume of distribution and therefore necessitate different "size-based" drug doses for different age groups. The product of these two factors, the clearance, allows the use of this single measure to estimate the appropriate drug dosage schedules according to $D/\tau = (C_{ss} \times Cl)/F$, where D stands for maintenance dose, τ for dosage interval, C_{ss} for steady state concentration and F for fraction absorbed into the central compartment. A literature review reveals data allowing the determination of the relationship of drug clearance (ml/hr/kg) versus age for such drugs as gentamicin, digoxin, sulfisoxazole, theophylline and others. Graphic presentation of these relationships shows that drug clearances (ml/hr/kg) are similar in newborns and adults, while between one and five years these clearances are much higher. This "toddler" peak explains in part the need for larger drug doses in this age group to achieve steady state drug concentrations which are identical to those found effective in adults receiving lower doses. This relationship allows appropriate size based drug therapy continuously for all developmental stages (ages).