277 PHARMACOKINETICS OF AMIKACIN IN CHILDREN; Edward B. Lewin and Chinh T. Le, (Spon. by Martin R. Klemperer) Univ. of Rochester School of Medicine and Dent., Strong Memorial Hospital, Department of Pediatrics, Rochester, N.Y.

Pharmacokinetics of aminoglycoside antibiotics vary both within and between different age groups. To determine proper dosing level and interval for children, sequential pharmacokinetics were studied in 10 patients ($\overline{age}$ = 8.7 yrs). All children had normal renal function. Mean weight and surface area were 29.5 kg and 0.99 m^2 respectively.

A dose of 7.5 mg/kg was administered IM q12h. Utilizing an acetyl transferase radioenzymatic assay, sequential serum levels were determined and were as follows (μg/ml $\pm$ SD): 0h=0; ½h=13.0 $\pm$ 4.0; 1h=12.2 $\pm$ 3.3; 2h=8.9 $\pm$ 3.3; 4h=3.1 $\pm$ 1.8; 6h=1.5 $\pm$ 1.3; 8h= $\leq$ 1.0. Drug was undetectable in serum after 8 hrs. No accumulation was observed. Mean peak serum: mean urine (0-12h) ratio was 1:20. There was no evidence of toxicity.

Utilizing this dosage regimen, the $t_{\frac{1}{2}}$ in our patients (1.7h) was 23% shorter than that in adult subjects (2.2h). The mean peak serum level (13μg/ml) was 35% lower than in adults (20μg/ml).

These data suggest that children require larger doses of amikacin administered at more frequent intervals than those utilized in this study.

278 AMINOGLYCOSIDE NEPHROTOXICITY, Paul S. Lietman, Johns Hopkins University School of Medicine, Department of Pediatrics, Baltimore, Md.

As a consequence of our previous studies defining the incidence of nephrotoxicity associated with gentamicin and amikacin, the pharmacokinetics of amikacin in children, and the marked accumulation of gentamicin and amikacin by human renal tissue, we have investigated some aspects of the phenomenon of renal accumulation of aminoglycosides in murine in vivo and in vitro systems. After a single intraperitoneal dose of gentamicin, there is a striking accumulation of the drug in the kidney (but not in several other tissues) and a markedly prolonged retention within the kidney (as compared with the rapid elimination from the plasma). The accumulated gentamicin is localized within kidney cells and distributed among several subcellular fractions. Based on dialysis and equilibrium dialysis, the accumulation does not appear to be accounted for by binding within the cells but rather seems to be dependent on transport into the cells. An in vitro kidney tubule preparation has been used to characterize some aspects of the uptake of gentamicin by renal tubular cells.

279 MULTIPLICITY OF CYTOCHROMES P-450 DURING DEVELOPMENT. David K. Manchester and Allen H. Neims. Roche Developmental Pharmacol. Unit, McGill Univ., Montreal.

Drug oxidations are catalyzed by the cytochromes P-450 monooxygenase complex. Livers of induced adult animals possess multiple forms of the hemoprotein component (P-450s) with distinct substrate and product specificities (Mol. Pharmacol., 11:874, 1975). Prompted by (1) a difference in neonatal pharmacokinetic profiles between caffeine and theophylline and most other 'oxidized' drugs (phenytoin, etc.) and (2) a reported difference in the substrate specificity of human fetal and adult hepatic monooxygenase activity, we are assessing individual P-450s in untreated and developing organisms. Hepatic microsomes from adult or 72-hr guinea pigs are treated for 3 hrs at 23° in a buffer containing glycerol, cholate, and Emulgen 911, a nonionic detergent. The solubilized P-450s, measured by CO binding, have mol. wts. of ca. 50,000 upon gel filtration. These P-450s can be separated from other hemoproteins and resolved into 4 peaks by DE52 chromatography with ca. 50% recovery. Each peak, when isoelectrically focused in polyacrylamide gels, can be further resolved into multiple protein bands, 2-4 of which stain for heme. Mixing experiments support this multiplicity. Similar results are obtained with adult rat liver microsomes. Guinea pigs, which exhibit substantial increases in hepatic monooxygenase activity within 72 hrs of birth also exhibit at this time multiple forms of P-450s as assessed by the above methods. Comparisons of gels and elution patterns of adult and 72 hr solubilized P-450s suggest that the relative proportions of multiple forms vary during development.

280 HEARING FUNCTION AND MATERNAL HEROIN ADDICTION. Dianne H. Meyer, Gilberto R. Pereira (Spon. by Sumner Yaffe) Dept. of Peds. & Oto-Laryn., of Rush Presbyterian St. Luke's Medical Center, Chicago, Ill.

Heroin addiction was considered a high risk factor for hearing loss for a mother and her developing fetus due to well-known ototoxic effects of quinine, a common additive to heroin sold to addicts. 21 infants and their heroin addicted mothers were evaluated for auditory impairment from March 1974 through June 1976. Characteristics of the study population were: age of infants: 5 days to 34 months (mean 7.2 + SD 10.2 mo); age of mothers: 21 to 29 years (mean 24.3 yr + SD 3.4 yr); maternal length of addiction 1 to 12 years (mean 3.2 + SD 3.43 yr); and daily habit cost: $5 to $150 (mean $40 + SD $43). All mothers studied whc were on methadone replacement programs (13) admitted to the infrequent but constant use of heroin throughout the pregnancy. A control group of infants and their non-addicted mothers were matched by age to the study infants. Evaluation in all subjects consisted of case history information, otological examination and standard audiological techniques. According to their ages, infants were tested by a neonatal screening test or by a soundfield audiometry or by play audiometry. The study showed no evidence of hearing impairment in either the addicted mothers or their infants. Although they were considered normal, responses of 6 addicted neonates were depressed as compared to their matched control possibly due to their use of phenobarbital. Maternal heroin addiction did not seem to represent a high risk factor for hearing loss in this population possibly because quinine exposure had not reached toxic levels.

281 HYDROCHLOROTHIAZIDE (HCT) THERAPY IN HYPERTENSIVE (HT) AND RENAL INSUFFICIENT (RI) CHILDREN: ELIMINATION KINETICS AND METABOLIC EFFECTS. Bernard Mirkin, Alan Sinaiko, Mehroo Cooper, and Marion Anders. Univ. of Minnesota, Div. Clinical Pharmacology, Minneapolis, MN.

The interrelationships between electrolyte and uric acid metabolism, renal function and HCT pharmacokinetics have been studied to determine whether modifications in current dosing practices would be beneficial in HT or RI children.

Outpatients (OP) on chronic HCT therapy received one-half their daily dose (0.6-2.75 mg/kg) in the morning and steady state HCT, Na, K, creatinine, BUN and uric acid levels determined. Inpatients (IP) received a single HCT dose on a fixed protocol. Blood specimens were obtained at 0,1,2,4,8,12 and 24 hours and urine specimens at 0-2,2-4,4-8,8-12 and 12-24 hours. HCT was assayed by high pressure liquid chromatography.

Serum HCT levels varied directly with dosage and inversely with Ccr. When Ccr exceeded 70 ml/min, OP receiving 1-1.5 mg/kg had HCT levels ranging from 130-190 µg/ml whereas levels between 260-600 µg/ml were found with doses of 2.0-2.75 mg/kg. When Ccr was below 50 ml/min extraordinarily high HCT levels (1000-4000 µg/ml) were observed even with doses less than 1.0 mg/ml. Serum half-life and elimination rates were inversely proportional to renal clearance in IP.

These data suggest that HCT accumulates in RI patients if no dosage adjustment is made. No positive correlation was established between elevated serum HCT levels and adverse reactions. (Supported by USPHS Grant HD-08580.)

282 RADIOIMMUNOASSAY (RIA) FOR THEOPHYLLINE AND CAFFEINE: APPLICATION TO STUDIES IN THE FETUS AND NEWBORN. Allen L. Neese and Lester F. Soyka, Univ. of Vermont College of Medicine, Dept. of Pharmacology, Burlington, VT

Use of theophylline (T) for apnea prompted development of a rapid, sensitive, selective microassay. Antiserum was raised in a goat, characterized, found to be highly specific for T and sensitive to 2 ng. Affinity of the antiserum and it's titer allowed routine assay of 2 ul plasma samples. The assay also has been adapted for use with 6 mm whole blood spots on filter paper. Plasma T levels two hours after 4 mg/kg per rectum maintenance doses (after loading doses of 8 mg/kg of aminophylline) ranged from 6-20 ug/ml (N=14). Terminal half-lives ranged from 12-54 hrs (30±5 hr, N=6). Cord samples from 75 consecutive deliveries were assayed for T and for caffeine (C) with antiserum supplied by C. E. Cook, Research Triangle Inst.; T ranged from 0.04 to 2.9 and C from 0.01 to 3.4 ug/ml, distributed as follows:

Serum Conc. (ug/ml)	T	C
<0.5	47%	28%
0.5 - 1.0	40	20
1.0 - 2.0	8	35
>2.0	5	17

Conclusions: RIA is a valuable method for assay of methylxanthines. Doses of T used in this study produced plasma levels which appear to be safe and effective. T half-life is variable and markedly prolonged in prematures, in agreement with studies using other assay methods. At least 50% of our perinatal population is exposed to C levels known to be pharmacologically active in adults.