253 DEVELOPMENT OF CALCIUM TRANSPORT IN THE JEJUNUM + ILEUM OF RATS. M.K. Younoszai and J. Ranshaw. College of Med., Univ. of Iowa Hosp., Dept. of Pediatrics, Iowa City, Iowa.

The greater intestinal absorption of calcium(Ca) in younger than in older rats could be associated with increased lumen-to-mucosa(LM) and/or decreased mucosa-to-lumen(ML) flux of Ca. We determined net absorption (NA) of Ca in the intestine of 1, 2, 3, 4 and 6 week old rats. The jejunum + ileum was perfused in situ with a solution containing per liter 3.4 mmole of ^{40}Ca, 145 mmole of NaCl, and 20 mg of Phenol Red. Tracer ^{45}Ca was added to determine LM flux. ML flux was calculated as the difference between LM flux and NA. As expected NA of Ca (μmoles/g dry weight/hr) was greater in suckling than in older rats (Mean±SE; 1wk, 18±4; 3wk, 16±3; 6wk, 3±2). LM flux was around twice NA and greater in the suckling rats (1wk, 45±5; 3wk, 28±3; 6wk, 8±1). ML flux was also greater in the suckling rats (1wk, 27±3; 3wk, 12±2; 6wk, 5±2). Thus the increased net Ca absorption in the suckling than in the older rats seemed to be the result of markedly enhanced unidirectional fluxes of Ca across the intestinal mucosa. These findings could be explained on the basis of greater permeability of the intestinal mucosa to Ca in suckling than in older rats. However, it is possible that the activity of the mechanisms involved in transport of Ca decreases with age in rats.

DEVELOPMENTAL PHARMACOLOGY

254 PHARMACOKINETIC DISPOSITION OF CAFFEINE IN PREMATURE NEONATES WITH APNEA. Jacob V. Aranda*, Winifred Gorman*, Eugene W. Outerbridge*, Allen H. Neims. Dept of Newborn Medicine, Montreal Children's Hospital and Roche Developmental Pharmacology Unit, McGill University, Montreal, Quebec.

The newborn infant is exposed to caffeine either transplacentally or postnatallv for the treatment of apnea. Using a one-compartment model, the pharmacokinetic disposition of caffeine in the neonate was determined. Caffeine (as the citrate salt) was given to 10 premature infants with apnea at a dose of 5 to 20 mg/kg via intravenous infusion for 10 to 20 min. Caffeine was measured in 10 μl of plasma by radioimmunoassay (Cook, Research Triangle Park, N.C). Blood samples were obtained by heelsticks at 2 to 8h interval for 72 to 86h. Pelative to adult whose $T\frac{1}{2}$ is 3 to 5h, caffeine was eliminated slowly.

	Post Natal Age (d)	Gest Age Wks	Birth Weight (g)	Dose (mg/kg)	$C_p o$ (mg/l)	AV_d (l/kg)	$T\frac{1}{2}$ (h)	Kel (h^{-1})	Clearance $ml.kg^{-1}.h^{-1}$
$\bar{x}$	9.2	28.4	1112.2	10.2	11.5	0.898	97.5	0.010	8.9
±	±	±	±	±	±	±	±	±	±
SE	1.5	1.0	111.3	1.2	1.9	0.072	20.2	0.002	1.7

Neither AV_d, $T\frac{1}{2}$, kel nor clearance correlated with birth weight or postnatal, gestational or postconcentional age. The data show that a loading dose of 10 mg/kg of caffeine (or 20 mg/kg of caffeine citrate) achieves a peak plasma concentration (Cp) of 8 to 14 mg/L. Maintenance dose of 2.2 mg/kg/24 h maintained Cp of 10 mg/L. The 7-fold range of individual caffeine clearance makes monitoring of Cp mandatory during maintenance therapy for apnea.

255 THE RELATIONSHIP OF AGE TO THE DISTRIBUTION AND PHYSIOLOGIC EFFECTS OF DIGOXIN IN SHEEP. William Berman, Jr., Peter J. Ravenscroft, Lewis B. Sheiner, Michael A. Heymann, Kenneth L. Melmon, Abraham M. Rudolph, Univ Cal, SF, Dept Pediatrics and Clinical Pharmacology and Hershey Medical Center, Dept Pediatrics.

We studied tissue distribution of digoxin and its effects on myocardial performance and cardiac conduction in fetal and adult sheep. Catheters were inserted and ECG electrodes attached in 11 fetuses(109-129 d gestation)and 8 non pregnant ewes. Digoxin was infused to achieve steady state; ratio of pre-ejection period (PEP)to left ventricular ejection time(LVET), cardiac rhythm and PR interval were recorded. Digoxin concentrations were measured repeatedly in plasma,and in myocardium and midbrain after sacrifice. We achieved higher plasma digoxin concentrations in fetuses than in adult sheep, but tissue to plasma ratios were similar: midbrain/plasma~6.4 fetus, 5.3 adult; myocardium/plasma-87 fetus, 90 adult. Myocardial responses to digoxin were greater in ewes than in fetuses; a plasma digoxin concentration of 2 ng/ml reduced PEP/LVET by 0.1 in ewes, but by only 0.06 in fetuses. Cardiac rhythm disturbances occurred in 6 of 8 ewes at an average plasma digoxin concentration of 2.3 ng/ml but in only one fetus, at a plasma digoxin concentration of 9 ng/ml. PR interval prolongation was linearly related to plasma digoxin concentration in fetuses but uncommon below a plasma digoxin level of 2 ng/ml in ewes. These studies show the effects of digoxin vary with age because of differences in tissue sensitivity rather than drug kinetics and provide experimental support for high concentration digoxin therapy in young infants.

256 PREDICTORS OF GENTAMICIN EXCRETION IN SICK NEWBORNS. Betty Bernard, Salvador J. Garcia-Cázares, Nancy Cheney, Roger W. Jelliffe (Spon. by Paul Y.K. Wu). Univ. of So. Calif. Sch. of Med., LAC-USC Med. Ctr., Depts. of Peds. and Med., Los Angeles, Calif.

To improve gentamicin (GMS) dosage regimens in neonates, data from 46 infants requiring GMS therapy were analyzed for K2 (.693/half-time) using the model:

Dose K1, Body Volume of Distribution (Vd) K2, Excretion.

K1=1.8 $hours^{-1}$ and Vd=14.7% of body weight.

K2 ($hrs.^{-1}$) was calculated to fit the serum level found. The patients were 1-14 days old (mean 5.5), with a gestational age (GA) of 29-42 weeks (mean 37.9) and a serum creatinine of ≥0.5 mg/dl. A serum GMS level was drawn 3-12 hours into the dose interval.

Fourteen clinical parameters were examined by stepwise multiple regression (SBC Call-370 Statpack). Estimated creatinine clearance (CCr), computed as described earlier by this laboratory, was 6-34 ml/min./1.73 M^2 (mean 17) and correlated best with K2. Other predictors, in order, were weight/length percentile (WL), GA, age (A) and sex (S, female=0, male=1). K2=.32838 + .00276CCr -.00167WL + .01792GA + .01893A -.07038S (r=.553, S.E.E.=137, P<.001). Based on this data, GMS half-time ranged from 0.81 to 5.13 hours with a mean of 1.82 hours. These findings have been incorporated into a computer program to permit computation of K2 for GMS with reasonable accuracy to allow initial or subsequent planning of GMS dosage regimens for sick newborn infants.
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257 TOXICITY FROM TEA INGESTION IN AN INFANT: A COMPUTER SIMULATION ANALYSIS. Andrew S. Brem, Horace Martin, and Leo Stern. Brown University, and Rhode Island Hospital, Departments of Pediatrics and Biochemistry, Providence, Rhode Island.

A seven week old previously healthy infant presented with tonic posturing and central nervous system irritability after concentrated tea ingestion. Using a gas chromatographic analysis technique, a sample of similarly prepared tea was examined for levels of caffeine, theophylline, and theobromine. Caffeine was the only xanthine found in the tea. A simulation of caffeine absorption and elimination was performed on a computer utilizing Euler's method on a three compartment model consisting of caffeine in the gut, in the body water, and caffeine excreted. Convulsions after caffeine administration have been reported at doses of 7 mg/kg. In our patient, the total estimated ingested dose of caffeine was 75 mg or 14.7 mg/kg with a maximum predicted blood level at 3 2/3 hours. A xanthine blood level from the infant at 5 hours was 1.1 mg/100 ml compared to a computer predicted value of 1.3 mg/100 ml. Computer simulation may be utilized to predict the pharmacologic course and distribution of ingested agents.

258 PLASMA AND BRAIN LEVELS OF PHENOBARBITAL AND DIPHENYLHYDANTOIN IN NEONATES WITH SEIZURES. Gertrude S. Carter, Michael J. Painter, and Charles Pippinger. (Spon. by Thomas P. Foley, Jr.) University of Pittsburgh, Magee Womens Hospital, Children's Hospital of Pittsburgh, Department of Pediatrics, Pittsburgh, and Columbia Presbyterian University, Neurological Institute of New York, New York.

Utilizing the EMIT system we have determined phenobarbital and diphenylhydantoin levels in 77 neonates with seizures. In addition, brain tissue was obtained for diphenylhydantoin and phenobarbital levels in ten neonates coming to autopsy.

Following intravenous loading doses of 15-20 mg/kg of phenobarbital, levels of 19.4 ± 3.4 mg/L were achieved. The volume of distribution of phenobarbital was 0.97 ± 0.20 L/kg and was not influenced by gestational age. Following intravenous loading doses of 15-20 mg/kg of diphenylhydantoin, levels of 14.9 ± 2.8 mgm/L were achieved. The volume of distribution of diphenylhydantoin was 1.19 ± 0.19 L/kg.

Maintenance doses of 5 mg/kg/d IV, IM or PO phenobarbital or 5 mg/kg/d IV diphenylhydantoin resulted in accumulation of each agent in the first seven days of therapy.

Although the volume of distribution of both agents is significantly greater in the newborn than the adult, the brain to plasma ratio was significantly less in the newborn.

It would appear that therapeutic brain concentrations of phenobarbital and diphenylhydantoin are difficult to achieve even when large loading doses of these agents are used.