259

CLINICAL AND PHARMACOLOGICAL EVALUATION OF CEFAMANDOLE (CM) IN PEDIATRIC PATIENTS INCLUDING NEONATES. C.T. Chang, M.M. Agbayani, A.J. Khan, L. Glass and H.E. Evans, Jewish Hospital and Medical Center of Brooklyn, Department of Pediatrics, Brooklyn, New York.

CM a new cephalosporin (CSP) is more active against common pathogens than other CSP antibiotics. Nine cases of pneumonia (PN) and 10 with UTI (average age 5 1/2 years) received an average dose of 25 mg/kg IM every 3 hours for an average of 8.3 days. In addition 12 full term newborn (NB) infants treated with antibiotic (s) for sepsis, were given 33 mg/kg of CM (IM in 7 and IV in 5) as one single dose. All cases of PN improved rapidly and urine in UTI cases became sterile by 3rd day and remained so for 24 hours in all and up to 6 weeks in 6. No clinical signs of toxicity were observed. 9 children had transient mild elevation of SGOT and one of BUN. Single doses (mg/kg) of CM gave following average serum levels ($\mu\text{g/ml}$).

	Route #	Dose	0'	15'	30'	1 hr.	2 hr.	4 hr.
Children	IM (2)	29	0	-	29.8	17	-	0.9
(4)	IV (2)	30.5	0.6	82.5	-	17	-	0.4
Newborn	IM (4)	33	1.4	-	44.5	24.5	14.5	9.4
(7)	IV (3)	33	0.4	50	38.5	30.3	-	7.6

At 15' after injection, blood levels were lower in NB than in children, but increased rapidly and were high at 4 hrs. Blood levels with CM are adequate and higher and prolonged in NB. It appears to be safe and effective in the treatment of PN and UTI. The data should encourage further evaluation of the efficacy and hepatic and renal toxicities in NB.

260

PROPRANOLOL ADMINISTRATION IN INFANCY. Carol M. Cottrill, Russell G. McAllister, Jacqueline A. Noonan, University of Kentucky College of Medicine, Department of Pediatrics, Lexington, Kentucky.

Propranolol, (P) the beta blocking agent has been used for treatment of arrhythmia and hypercyanotic spells in infancy. Very little firm data about pharmacologic parameters is available. This series involves P levels in 6 infants. One infant, born to a mother treated with 160 mg P/day had P levels which increased over the first 4 hrs. of life. Two newborns with atrial arrhythmia refractory to Digoxin were begun on small doses of P which were increased until a therapeutic result was obtained (at a dose of 1 mg/kg/24 hr.). Three infants ranging in age from 7-11 mos. (wgt. 7-9 kg.) were treated with 2.5 mg/kg/24 hr. in 4 divided oral doses for hypercyanotic spells. Serial (P) levels were obtained from 45 min. to 6 hrs. following the oral dose and these levels were incorporated into a curve from which the half-life (2.3 hrs.), the elimination, constant (0.005 min.⁻¹) and the volume of distribution (8.13L/kg) of the drug were calculated. The P level decrease with respect to time was a straight line function which yielded a correlation coefficient of 0.93. These values are identical with those from pharmacokinetic studies in adults. Conclusions: (1) Infants > 7 mos.; > 7 kg. on 2.5 mg/kg/24 hr. metabolize, distribute, and eliminate P as adults. (2) In the neonate, these values may not apply and a dose of 1 mg/kg/24 hr. was therapeutic. (3) Given to pregnant women, the drug is stored in the fetal liver and the increased level reflects the inability of the fetus to adequately metabolize the drug.

261

SERIAL PLASMA (PChE) AND RED CELL CHOLINESTERASE (AChE) LEVELS OF SCHOOL CHILDREN FROM A FOREST INSECTICIDE SPRAY AREA IN CANADA. John F. Crocker, Donald J. Ecobichon and Rodney M. Bergh. Departments of Pediatrics and Pharmacology, Dalhousie University, Halifax, N.S., Can.

Noting a geographical clustering of Reye's syndrome in a forest insecticide spray area, a seasonal study of plasma (PChE) and red cell cholinesterase (AChE) levels in children living contiguous to the forest spray area has been carried out. PChE and AChE are standard indices for the toxicological effect of organophosphate and carbamate insecticides. Serial samples of heparinized blood were collected in March, June and October from 100 children and assayed for PChE and AChE, with the following results:

	March	June	October
PChE($\mu\text{mole/ml/min}$)	3.57S.D.0.75	3.28S.D.0.62	3.23S.D.0.77
AChE($\mu\text{mole/ml/min}$)	14.29S.D.2.48	14.26S.D.1.83	18.49S.D.3.71

PChE levels were significantly different between March and June ($p < 0.01$) with no significant difference between June and October. AChE levels on the other hand do not vary significantly between March and June but are significantly higher in October ($p < 0.001$). Forest spraying was done from May until June with an organophosphate, emulsifier and solvent combination.

The depression of PChE during and after completion of the spraying program compared to PChE levels in the late winter furnishes biochemical evidence of chemical exposure to insecticides in areas adjacent to forest areas subjected to large scale spraying with insecticides. A similar effect on AChE levels was not observed.

262

MAGNESIUM LEVELS IN INFANTS OF MOTHERS TREATED WITH MgSO₄. Barbara C. Dangman & Tove S. Rosen, Dept. of Ped. Coll. of P&S, Col. Univ., N.Y. Spons. by L.S. James

MgSO₄ remains a commonly used therapy for obstetric patients with pre-eclampsia or premature labor, but little is known of its effects on the newborn. We studied plasma magnesium (Mg) levels and urinary excretion of Mg during the first 7 days of life in 16 premature and 5 full term infants of mothers treated with Mg. Clinical symptomatology consisted of mild hypotonia in 11 cases and did not correlate with peak plasma levels. The maternal plasma Mg level at delivery was 4.2 ± 0.28 mg/dl (M $\pm$ SE) and the ratio of maternal to umbilical artery (UA) values was 1.14. The infants' plasma Mg rose from 3.68 ± 0.20 mg/dl (UA) to 4.2 ± 0.17 mg/dl at 2 hrs. of age (heel stick). Subsequent levels showed a linear plasma elimination with a correlation coefficient of -0.9533. The plasma $t_{1/2}$ was 43.22 hrs. Levels did not reach a normal range (1.5 - 2.5 mg/dl) until approximately 1 week of age. There were no significant differences in either peak plasma levels or rate of elimination between the following subgroups: infants of mothers 1) receiving a total of >50 gm vs <50 gm; 2) receiving MgSO₄ for >24 hrs vs <24 hrs; 3) receiving Mg infusions at a rate of >1.5 gm/hr vs <1.5 gm/hr; 4) with plasma Mg concentrations >4 mg/dl vs <4 mg/dl; 5) who had pre-eclampsia vs those treated for premature labor only; and 6) premature vs full term infants. Urinary clearance (Mg/creatinine) varied widely and failed to show any consistent association with either plasma level or postnatal age. Thus Mg, in the doses administered and at the plasma concentrations attained, has a prolonged $t_{1/2}$, but does not exert any major deleterious effects on the newborn.

263

AEROSOLIZED GENTAMICIN IN CYSTIC FIBROSIS: Michele A. Danish, Allan Arbeter, Mary Rosenlund, Sumner J. Yaffe, Univ. of Pennsylvania Sch. of Med., Children's Hospital of Philadelphia, Dept. of Ped., Philadelphia, Pa.

Persistent colonization of the respiratory tract with ps. aerug. is a major problem in children with cystic fibrosis (CF). Because gentamicin penetration of CF sputum is inadequate after parenteral administration, we undertook an investigation of the safety and efficacy of gentamicin aerosol. Nine CF children (5F, 4M) ages 6-15 years with moderately severe disease were studied. Following baseline pulmonary and microbial studies, each child received 40 mg of gentamicin sulfate by nebulization three times daily for one week. Gentamicin disposition and pulmonary function were studied initially and at the end of the treatment program. No adverse effects from the treatment were observed. Peak sputum concentrations of gentamicin varied from 3.6 to 18.5 mcg/ml after one dose to 6.4 to 33 mcg/ml after one week of therapy. Peak blood concentrations ranged from 0 to 0.35 mcg/ml initially and were somewhat higher at the end of the treatment program. Urinary concentrations were insignificant. The mean clearance of gentamicin from the sputum was 51 ml/min/1.73 m² (6 pts). Microbial studies in five patients demonstrated a striking decrease in pseudomonas colony counts. No strains developed resistance to gentamicin. Pulmonary function tests improved in 5 patients, showed no change in 3, and diminished in 1, perhaps in association with a clinical URI. All the children showed marked clinical improvement. These results provide a rationale for, and strongly warrant, a clinical trial of aerosolized gentamicin in CF patients.

264

CHRONIC PHENOBARBITAL ADMINISTRATION DURING INFANCY: EFFECTS UPON BRAIN DEVELOPMENT IN RATS. Jaime Diaz, Richard J. Schain. University of California, Depts. of Psychiatry, Neurology and Pediatrics, Los Angeles, CA 90024.

Recent studies in our laboratory have revealed that phenobarbital retards early brain growth. In these experiments the effect of chronic phenobarbital administration upon brain development was evaluated under isocaloric conditions of nutrient intake. Chronic intragastric cannulas were installed in 4 day old Wistar rat pups. From day 5 through day 18, these animals received daily subcutaneous injections of 60mg/kg of phenobarbital (n=15) or of the vehicle alone (n=12). An initial period of sedation was observed which gradually disappeared throughout the course of the experiment. On day 19, the animals were weighed and sacrificed. There were no significant differences in body weights between phenobarbital treated and control groups. There was a 12% reduction in brain weight of the phenobarbital treated animals compared to controls ($p < .001$). DNA, RNA, protein, and cholesterol contents in the experimental animals were significantly lowered in cerebrum. The cerebellum of these animals was affected to a lesser extent but also exhibited growth retardation. These data indicate that chronic phenobarbital administration in the pre-weanling rat selectively retards brain development.