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D-PENICILLAMINE (PCA): ITS ACTIONS ON LEAD-203(^{203}Pb) CHELATION IN BONE ORGAN CULTURE. John F. Rosen, Albert Einstein Coll. Med., Montefiore Hosp. & Med. Ctr., Dept. Ped., New York.

PCA is used often to treat Pb toxicity after administration of $CaNa_2EDTA$. Since the source of Pb mobilized by PCA comes from bone, this study was undertaken to define further PCA's actions on bone, after demonstration of a readily mobile compartment of skeletal Pb in vitro regulated like bone mineral. Pregnant rats were injected with 500 μCi of ^{203}Pb and 200 μCi of ^{45}Ca on the 18th day of pregnancy. On day #19, paired fetal bones were cultured in a chemically defined medium to which PCA, parathyroid hormone (PTH) or 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) were added. For 48 to 120H, bones were maintained in experimental media (EM); and the amount of ^{203}Pb released into the EM's was compared to that released into the appropriate control media (CM). The results (* = $p < .01$, different from 1.00) were expressed as cpm EM/CM ratios: PCA (1.00mM) 1.96±.04*; PCA + PTH 6.30±.14*; PCA + $1,25(OH)_2D_3$ 5.89±.10*. Increasing and decreasing medium levels of Ca and phosphate depressed and enhanced ^{203}Pb release, respectively, while no effect on ^{45}Ca release was seen with PCA alone. PCA, compared to equimolar amounts of $CaNa_2EDTA$, was 1000 times less potent in chelating ^{203}Pb; and PCA's maximum effect was transient vs. $CaNa_2EDTA$ (48 vs. 120H).

These data indicate that PCA, like $CaNa_2EDTA$, produce ^{203}Pb release from a rapidly mobile compartment of bone Pb; but PCA's action was less potent and short-lived compared to $CaNa_2EDTA$.

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INFLUENCE OF DEXAMETHASONE AND ACTH ON DRUG CLEARANCE IN CHILDREN. P. Saenger, A. Rifkind, J. Pareira, L.S.Levine, M.I.New. Cornell University Medical College, New York.

The rate of disappearance of antipyrine from the plasma is a useful indicator for the in vivo capacity for hepatic mixed function oxidation. The short term effects of systemic administration of dexamethasone, a potent glucocorticoid, and ACTH on antipyrine metabolism were studied in 10 children. Dexamethasone (2 mg/d X 4 days) was given to 6 subjects. The effects of ACTH (40 U/24 h i.v. X 5 days) were evaluated in 4 patients. The half-life of antipyrine ($t_{1/2}$) was measured before and after drug therapy in each patient. The mean $t_{1/2}$ was not affected by administration of dexamethasone ($t_{1/2}$ 7.6 ± 1.14 h versus 7.8 ± 0.84 h). The apparent volume of distribution (aVd) remained unchanged as well (aVd 0.52 ± 0.076 L/kg versus 0.56 ± 0.063 L/kg). Administration of ACTH, causing a 5-25 fold increase in urinary 17-hydroxy-corticosteroid excretion, also did not affect the half-life of antipyrine ($t_{1/2}$ 11.5 ± 2.8 h versus 11.2 ± 2 h). The aVd also remained unchanged (0.60 ± 0.05 L/kg versus 0.59 ± 0.03 L/kg). We conclude that the short term administration of dexamethasone and ACTH with ensuing stimulation of endogenous glucocorticoid production is unlikely to produce clinically significant changes in the rate of drug metabolism.

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NETILMICIN PHARMACOLOGY IN PEDIATRIC PATIENTS. V. Schauf, V. Chindasilpa, L. Hamilton, and L. Riff. Univ. of Ill. Hospital, Dept. of Peds and Med. Chicago

Netilmicin, an aminoglycoside with spectrum similar to gentamicin, is less toxic than gentamicin in animals, and is safe and efficacious in adults. We studied netilmicin in 40 infants and children with suspected or proved bacterial infection. Most patients also received a penicillin. In newborns, one hour after the first IM dose a peak level of 2.9±.4 mcg/ml was achieved; $T\text{-}\frac{1}{2}$ averaged 3.85 h. The peak levels attained after the first dose were suboptimal. However, levels on the 2nd d of therapy were 4.5±.6 mcg/ml and on day 7-10, the peak level was 4.6±1.0 mcg/ml. In infants > 7 d. of age, $T\text{-}\frac{1}{2}$ averaged 3.0 h. Serum concentration curves on day 7-10 were higher than those observed after the first dose but significant drug accumulation did not occur between the 2nd and 10th d. Peak values did not vary with age. The time to reach the trough level was 11 h in infants < 1 wk, but 7 h in patients > 1 wk. Anuric patients had prolonged elevation of serum concentrations. Measurable netilmicin levels were found in CSF, ascites fluid, kidney, muscle, and spleen. EEG or pure tone audiometry was normal in all 26 patients tested. No renal abnormalities were attributable to netilmicin use. Eosinophilia occurred in 17 patients. Documented bacterial infections were successfully treated with netilmicin alone (4) or in combination with other antibiotics (9). In light of the predictability of serum levels, efficacy, and minimal toxicity, a controlled comparative study of netilmicin with other aminoglycosides should be undertaken.

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INFLUENCE OF MATERNAL METHADONE AND HEROIN USE ON NEONATAL WITHDRAWAL. Elsa Sell, Nancy Bradley, Kathy Kale, and Bill Longwell. (Spon. by Grant Morrow) University of Arizona, Health Sciences Center, Department of Pediatrics and Hope Center, Tucson.

Infants of 23 mothers on a methadone maintenance program were observed for evidence of drug withdrawal. Ten infants had no withdrawal; 13 had withdrawal symptoms and 9 required treatment. The mothers' highest methadone doses ranged from 7½-80 mg, and their lowest doses ranged from 0-40 mg. Mothers who in the third trimester had 1/3 or more of weekly random urines positive for heroin or who were suspected by the center of heroin use (e.g. refusal to have urine tested), were defined as heroin users

In the 13 mothers not using heroin, only 3 infants (23%) had withdrawal symptoms. In the 10 mothers using heroin, all 10 infants had withdrawal symptoms. This difference is significant at $p < .001$.

When the mother's methadone dose at delivery was considered, the infants of 3 mothers who were on 15 mg or more of methadone and whose methadone dose had been increased before delivery, all exhibited withdrawal symptoms. In contrast, none of the infants of 10 mothers who were on <15 mg. methadone and had had no increase in dose before delivery showed withdrawal symptoms.

Conclusion: Mothers maintained on methadone during pregnancy had a greatly increased risk of delivering a symptomatic infant if they were also taking heroin during the third trimester, or if the methadone dosage had been increased prior to delivery.

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IMPAIRED PERFORMANCE AND "PARADOXICAL" HYPERACTIVITY DURING PHENOBARBITAL ADMINISTRATION TO DEVELOPING RAT PUPS WITH EXPERIMENTAL MINIMAL BRAIN DYSFUNCTION (MBD) Bennett A. Shaywitz, David A. Pearson, Departments of Pediatrics and Neurology, Yale University School of Medicine, New Haven. Phenobarbital may produce significant behavioral alterations and cognitive deficits in children and impaired brain growth in developing animals. We have investigated the long term consequences of phenobarbital administration on activity levels and cognitive performance in normal developing rat pups and littermates receiving intracisternal injections of 6-hydroxydopamine (6-OHDA) at 5 days of age. In normal rat pups, phenobarbital reduced activity levels at 26 days of age ($p < 0.05$), but did not affect avoidance performance. However, in 6-OHDA rat pups phenobarbital reduced activity at 19 days ($p < 0.001$) increased activity at 26 days of age ($p < 0.05$) and significant impaired both T-maze and shuttle box performance ($p < 0.001$). Phenobarbital concentrations at 35 days (EMID Technique) averaged 15.5 + 2.01 and 20.2 + 2.76 μg/ml in control and 6-OHDA rat pups respectively ($p > 0.05$). Body weight was significantly reduced in 6-OHDA rat pups from day 8 but there were never significant differences between phenobarbital and control animals. Brain dopamine concentrations in 6-OHDA animals averaged 35.5% of littermate controls and did not differ between phenobarbital and control animals. These findings support the notion that phenobarbital administration may adversely affect activity and cognitive performance in the developing mammalian brain and suggest caution in the routine use of this agent.

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EFFECT OF ENDOTOXIN ON RAT HEPATIC DRUG METABOLISM DURING DEVELOPMENT. Babasaheb R. Sonawane* and Sumner J. Yaffe. Children's Hospital and Dept. of Pediatrics, University of Pennsylvania, Philadelphia, PA 19104.

The frequency of gram negative infections and endotoxemia in the perinatal period prompted an investigation of the effects of endotoxin (E. coli. 026B6) on hepatic drug metabolism. Chronic dosing of endotoxin (0.2 mg/kg/d x 7 days) to lactating mothers significantly stimulated hepatic microsomal cytochrome P-450 (118%) and aminopyrine demethylase activity (114%). No alteration in neonatal enzyme activities was observed. Body and liver weight ratios or microsomal protein level of mothers and neonates were not altered by chronic administration of endotoxin to mothers during the experimental period. The acute i.p. administration of of endotoxin to mothers (1.4 mg/kg on the 7th day after parturition) significantly decreased the activity of aminopyrine demethylase (48%) and content of cytochrome P-450 (25%). When neonates themselves were injected (i.p.) with endotoxin (1.0 mg/kg) at 7, 16 and 27 days of age, a significant reduction in levels of mixed function oxidase enzymes was observed. Cytochrome P-450 contents were reduced by 57, 32 and 24% and aminopyrine demethylation decreased by 78, 48 and 34% in 7, 16 and 27 day old animals resptively. These observations indicate that the ability of mothers and neonates to metabolize drugs is significantly decreased upon acute exposure to endotoxin and this demands careful evaluation of drug disposition in gram negative sepsis during perinatal period. Supported by NIH Grant HD 10063.