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TOBRAMYCIN VERSUS GENTAMICIN FOR THE NEONATE.

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Tobramycin produces less serum creatinine increase than gentamicin in adults, suggesting that tobramycin may be less nephrotoxic and safer than gentamicin. The frequent use of aminoglycosides in the neonate led us to compare these agents to determine if tobramycin offers an advantage in safety for the neonate. This randomized, double-blind comparison included infants ≤ 3 d age without known renal disease treated a mean of 7.5d with gentamicin (20) or 8d with tobramycin (30). Infants received 2.5mg/kg/12h aminoglycoside. The groups were comparable for gestational age, underlying diseases, apgar score, and clinical condition. After at least one day of therapy the peak serum level was 5.4 μ g/ml tobramycin and 5.9 μ g/ml gentamicin and the trough level was 1.8 μ g/ml tobramycin and 2.3 μ g/ml gentamicin. There was no significant difference between tobramycin and gentamicin in the frequency of proteinuria, glucosuria, hematuria, casts or serum creatinine increase of over .4mg% during therapy. Definite nephrotoxicity occurred in 10% of each group. The tobramycin group showed lower average serum creatinine by .3mg% and higher creatinine clearance by 7ml/min/1.73m² both during and after therapy. After therapy, urine N-acetyl- β -glucosaminidase was .09 $\pm$.02 IU/mg creatinine for tobramycin and .24 $\pm$.09 IU/mg creatinine for gentamicin. Although tobramycin use resulted in a small improvement in creatinine clearance and less enzymuria, the clinical significance of these observations appears minimal.

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CELLULAR PHARMACOLOGY OF ANTIBIOTICS USED TO TREAT H. INFLUENZAE TYPE B (Hib) INFECTIONS. Richard F. Jacobs, Chris B. Wilson, Judy Laxton, Arnold L. Smith, Univ.

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Cellular antibiotic distribution is an important aspect of drug pharmacology. We confirmed Fothergill's observation that Hib may remain viable within polymorphonuclear leukocytes (PMN) and examined the ability of relevant antibiotics to enter PMN and to kill intracellular Hib. PMN were exposed to relevant concentrations (30 μ M) of ¹⁴C-penicillin G (Pen) or ¹⁴C-chloramphenicol (Cm). At intervals cells were separated from the incubation mixture by centrifugation over silicone oil. Intracellular and residual extracellular water content of PMN were determined by parallel incubation of cells in ³H-H₂O or ³⁵S-Na₂SO₄. The cellular to extracellular ratio for Pen was 0.14 $\pm$ 0.18 (n=5) and for Cm was 3.32 $\pm$ 0.32 (n=6). Cellular uptake of Cm was not dependent on PMN energy or inhibited by non-radiolabelled drug. PMN were allowed to ingest opsonized Hib for 30 min and extracellular Hib were removed by differential centrifugation. At this time PMN contained 4 log₁₀ viable Hib. 24 hr incubation in Pen or Ampicillin (Amp) at 4, 10 and 40 X minimum bactericidal concentration (MBC) resulted in a 0.5 to 1 log₁₀ reduction in Hib; whereas, 24 hr incubation in Cm resulted in a 2.3, 2.5 and 3 log₁₀ reduction in Hib at 4, 10 and 40 X MBC. The 0.5 to 1 log₁₀ reduction by Pen and Amp was due to killing of residual extracellular Hib. Thus, lipid soluble antibiotics such as CM that are concentrated and remain active within PMN may have significant pharmacologic advantages at a cellular level.

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A COMPARISON OF THE PHARMACOKINETICS OF NETILMICIN AND GENTAMICIN IN NEWBORNS. N.R. Joye, C. Halsted, and R. Adelman. Dept. of Pediatrics, University of California, Davis, Davis, California.

In a prospective double-blind randomized study, 20 newborn infants were given either NT or GT IV 5mg/kg/day, q 12h for presumed septicemia. After at least 4 doses of aminoglycoside antibiotic, serum samples were drawn prior to and 0.5, 2, 4, 8, and 12 hours after infusion. (Antibiotic concentrations in sera were determined by microbioassay).

The following were determined for each drug: t_{1/2}=half life, k_{el}=rate of elimination, Vp=apparent volume of central compartment C_{po}=theoretical concentration of aminoglycoside in plasma at t=0.

Drug	t _{1/2} (h)	k _{el} (h ⁻¹)	Vp(L/kg)	C _{po} (mcg/ml)
GT	5.53 $\pm$ 1.69	4 $\pm$.05	.28 $\pm$.06	10.1 $\pm$ 2.9
NT	6.47 $\pm$ 2.57	.21 $\pm$.05	.36 $\pm$.11	8.2 $\pm$ 3.4

There were no statistically significant differences in serum values at any time (see graph) or in pharmacokinetic parameters (see table.)

Our data indicate that the pharmacokinetics of netilmicin and gentamicin in the newborn are comparable.

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EFFECT OF ISOXSUPRINE ON β -ADRENERGIC RECEPTORS AND ADENYLATE CYCLASE IN FETAL RABBIT CARDIAC MEMBRANES. Vallop Kanjanapone and Asha Puri. (spon. by Jeffrey J. Pomerance) UCLA School of Medicine, Cedars-Sinai Medical Center, Department of Pediatrics, Los Angeles, California.

Isoxsuprine (ISX) has been used in mothers with premature labor. To examine the effect of chronic exposure of ISX on fetal myocardium, eight doses of ISX (3 mg/kg) were injected intramuscularly into pregnant rabbits between 24-27 days gestation. At 28 days, fetal cardiac membranes were examined for β -adrenergic receptors (β AR) by (-)-[³H]dihydroalprenolol (DHA) binding and assayed for adenylate cyclase (AC) activity. There was no difference in mean fetal heart weights in saline and ISX treated groups. (-)-[³H]DHA binding sites were rapid (t_{1/2}<30 sec.), reversible (t_{1/2}>90 sec.) and saturable with high affinity and low capacity. β -adrenergic agonists and antagonists competed for these sites and had characteristics of β_1 -subtype of β AR. Chronic ISX treatment led to a decrease in the mean $\pm$ SEM of maximal (-)-[³H]DHA bound from 126 $\pm$ 7 fmoles/mg (n=6) to 64% of the control value, 81 $\pm$ 8 fmoles/mg (n=6) (p<.01), with no change in affinity (K_d=1.8 $\pm$ 0.2 vs. 2.4 $\pm$ 0.3 nM). In addition, AC stimulation by (-) isoproterenol (10 μ M) was reduced from 66.1 $\pm$ 4.2 pmoles cAMP/mg/15 min. (n=5) to 62% of the control response, 41.2 $\pm$ 4.1 pmoles cAMP/mg/15 min. (n=5) (p<.01) with no change in the basal activity in fetal cardiac membranes (24.5 $\pm$ 1.9 vs. 24 $\pm$ 0.9 pmoles cAMP/mg/15 min.).

Thus, chronic ISX exposure of rabbit fetuses downregulated the β AR density in fetal cardiac membranes at 28 days and was accompanied by diminution of the response of AC to isoproterenol stimulation.

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SERUM CONCENTRATIONS OF 9- β -D-ARABINOFURANOSYL-HYPOXANTHINE IN INFANTS TREATED WITH VIDARABINE.

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Vidarabine has recently been shown to significantly reduce mortality and morbidity in infants with herpes simplex virus infection. However, pharmacokinetic data in infants have not been available. Concentrations of Vidarabine (ara-A) and its major metabolite, 9- β -D-arabinofuranosylhypoxanthine (ara-HX) were serially measured in serum and urine on 10 occasions in 7 patients following a 12-hour infusion of ara-A. Doses ranged from 15-30 mg/kg. Blood samples were collected on ice into tubes containing 50 μ g pentostatin. Ara-A and ara-HX were measured by HPLC. Ara-A was not detected in serum or urine at any time in any patient. Serum concentrations of ara-HX at the end of the 12-hour infusion ranged from 3.8 μ g/ml to 11.4 μ g/ml. Concentrations of ara-HX in urine were 5-10 fold serum concentrations. There was no consistent correlation between dose and serum concentration of ara-HX. Estimated half-lives varied from 3.4 hours to 8.6 hours (mean = 6.5 hours) except in one infant with severe hepatic disease in whom the t_{1/2} was 16.2 hours. The mean t_{1/2} was longer than that reported in adults (3-4 hours). However, no accumulation occurred with the doses employed. Ara-A appears to be rapidly deaminated in infants as in adults so that the parent compound is not detected in serum or urine.

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BIOAVAILABILITY OF ORAL CHLORAMPHENICOL PALMITATE COMPARED TO INTRAVENOUS CHLORAMPHENICOL SUCCINATE.

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The relative bioavailability of intravenous (I.V.) chloramphenicol succinate (CAP-S) and oral chloramphenicol palmitate (CAP-P) was compared in 14 children ages 2 months to 8 years. Chloramphenicol and CAP-S were measured in serum and urine by HPLC. The area under the serum concentration vs time curve (AUC) of chloramphenicol and urinary excretion of CAP-S were determined in each child under steady-state conditions while receiving CAP-S and again while receiving CAP-P. In 12 of the 14 children AUC was greater during oral CAP-P therapy, in 1 patient AUC was unchanged, and in 1 patient AUC was slightly decreased during oral compared to I.V. therapy. The mean AUC was significantly greater during oral therapy compared to I.V. therapy (116.3 $\pm$ 6.8 mg.hrs/L vs 77.7 $\pm$ 9.1 mg.hrs/L, p<.005). The relative bioavailability of I.V. CAP-S was 67% compared to oral CAP-P. This was explained by a loss of 39% of the I.V. dose in the urine as unhydrolyzed CAP-S. The dose of I.V. CAP-S did not correlate with AUC (r=.247). However, there was a significant correlation between dose of oral CAP-P and AUC (r=.733, p<.005). The bioavailability of oral CAP-P is superior to I.V. CAP-S. Furthermore, there is a greater correlation between dose and amount of active drug in the body when the oral preparation is used. Oral CAP-P appears to offer significant therapeutic advantages in patients who can tolerate oral medication.