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NETILMICIN IN PREMATURE AND FULL-TERM INFANTS: ITS EFFECTS ON THE RENAL AND AUDITORY FUNCTIONS AND ITS KINETICS ACCORDING TO MULTICOMPARTMENT MODEL. Bruno

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68 neonates with gestational age ranging from 27 to 40 weeks, 6-15 days postnatal age and 800-3400 g birth weight were treated for 5-14 days with Netilmicin (N), 2.5 mg/kg/b.i.d. or t.i.d. according to postconceptional age. Their renal function was studied by measuring serum creatinine concentrations during and up to 15 days after therapy. The urinary excretion of N-acetyl-glucosaminidase (NAG) was measured as a marker of tubular injury. Valley N serum levels were monitored during the treatment. Serum and urinary washout profile of the drug were followed for up to 10-15 days after discontinuation. Behavioral and impedance audiometry are being performed between 6 to 12 months of age. Treatment with N (always in association with a β -lactam antibiotic) did not represent for the newborns a source of toxicity as far as either renal or auditory (38 infants so far examined) function are concerned. Small preterm neonates (≤ 34 weeks G.A.) more frequently had elevated valley serum N concentration (≥ 3 ug/ml). The serum and urinary washout followed a multiexponential decay with prolonged terminal T 1/2 indicating tissue accumulation.

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POPULATION PHARMACOKINETICS OF PHENOBARBITAL IN NEWBORNS DETERMINED BY NONMEM ANALYSIS. Thaddeus H. Grasela, Steven M. Donn, College of Pharmacy and Depts. of Pharmacy and Pediatrics, University of Michigan, Ann Arbor, MI. (Spon. by G.W. Goldstein).

Routine clinical pharmacokinetic (PK) data from 59 newborns, gestational ages 24-42 weeks (mean $\pm$ SD = 31 ± 4.1) and birthweights 600-3620 gm (mean $\pm$ SD = 1520 ± 700) who received anticonvulsant doses of phenobarbital (PB) were evaluated using NONMEM analysis. Fifty of these infants were less than 1800 gm and were treated for one week to prevent cerebral hemorrhage. Infants initially received 20 mg/kg of PB IV followed by maintenance doses of 2.5 mg/kg every 12 hours. Serum PB was measured 2 hours after loading and on days 3 and 6.

Mean serum PB concentration post-loading was 19.8 ± 3.7 (SD) μ g/ml. The mean apparent volume of distribution (AVd) was 0.96 ± 0.024 (SEM) L/kg with a coefficient of variation (CV) of 16%. Mean clearance was 0.08 ± 0.003 (SEM) ml/min/kg, with a CV of 19%. Calculated mean serum half-life was 140 hrs.

Within this population, neither gestational age nor birthweight had an effect on PK parameters. Asphyxia (5 min Apgar score < 5), on the other hand, had an effect on AVd, with a 13.7% increase noted in asphyxiated versus non-asphyxiated infants, $p < 0.05$.

We conclude: (1) NONMEM is an accurate and easily implemented method of population PK analysis in newborns, (2) inter-individual variability in AVd and clearance of PB is minimal in the first week of life, and (3) alterations in PK parameters of phenobarbital are seen in asphyxia, where increases in AVd may result in lower than expected serum concentrations.

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NONMEM: AN ALTERNATIVE TO TRADITIONAL PHARMACOKINETIC STUDIES IN PEDIATRIC POPULATIONS. Thaddeus H. Grasela, Steven M. Donn, College of Pharmacy and Departments of Pharmacy and Pediatrics, Section of Newborn Services, University of Michigan, Ann Arbor, MI. (Spon. by G.W. Goldstein).

Traditional pharmacokinetic studies provide valuable information for optimizing the clinical use of pharmacologic agents. These studies generally require careful and extensive sampling of blood from subjects to determine pharmacokinetic parameters, making them less useful and less feasible in pediatric practice. As a result, data from adult patients or volunteers are often erroneously extrapolated for pediatric use.

Sheiner et al (J Pharmacokin Biopharm 5:445, 1977) developed a computer program, NONMEM, to estimate population pharmacokinetic parameters from data generated during routine clinical care of patients. NONMEM uses the method of extended least squares and allows for pooling of data from many individuals, but explicitly adjusts for the correlation of data obtained from each individual. NONMEM's advantage is that it can be utilized when only a few blood samples are available from each patient, provided the overall size of the study population is large. Thus, NONMEM is an ideal method for estimating population pharmacokinetic parameters in the newborn and general pediatric populations, where the frequency and volume of sampling are important considerations. This will provide the capability to accurately determine population pharmacokinetic parameters for a number of potentially toxic drugs with which newborns and children are treated.

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DEVELOPMENTAL STUDY OF AMRINONE DISPOSITION IN INFANTS. Thomas P. Green, Thomas J. Kulik, Randal P. Marchessault, Dana E. Johnson, and James E. Lock, Dept. of Ped, U of Minnesota, Minneapolis, MN.

Amrinone (AMR) is an orally effective, positive inotropic agent and vasodilator unrelated pharmacologically to other available drugs, including catecholamines and cardiac glycosides. Clinical studies in adult subjects have demonstrated a close relationship between AMR plasma concentrations and improvement in cardiac index. The disposition of AMR was studied in 6 children (3 neonates and 3 infants < 12 mo) receiving the drug for pulmonary hypertension which was unresponsive to other vasodilators.

Subjects received doses of 1-3 mg/kg AMR iv and elimination kinetics were determined following the last dose. In this population the volume of distribution (1.54 ± 0.85 L/kg) and drug clearance rate (0.29 ± 0.21 L/kg/h) of AMR showed marked inter-individual variability. This was attributable to increases in volume of distribution ($r = 0.78$, $p < 0.1$) and drug clearance rate ($r = 0.91$, $p < 0.02$) with age. Elimination half-life was similar in neonates (4.9 ± 3.0 h) and infants (3.7 ± 0.8 h). Hemodynamic and oxymetric data suggested that AMR produced selective although transient pulmonary vasodilation in the infants but not in the neonates in this study. This difference in response occurred despite a trend to higher AMR peak serum concentrations in the neonatal group than in older infants (6.4 ± 4.1 μ g/ml vs. 3.5 ± 1.8 μ g/ml).

Important changes in pharmacokinetic and pharmacodynamic properties of AMR occur during the first year of life and will warrant therapeutic drug monitoring of AMR and similar compounds.

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CALCIUM CHANNEL BLOCKADE AS THE TREATMENT OF ENDOTOXIN SHOCK IN NEWBORN PUPPIES. Andrew J. Griffin, Masakatsu Goto, Earl P. Ow, Mohammed M. Sayeed. (Spon. by D. Vidyasagar). Loyola University Medical Center, Department of Pediatrics, Maywood, Illinois

Previous studies have shown that pretreatment of adult rats with the calcium channel blocker diltiazem (DZ) attenuates the Endotoxin (ET) induced decrease in cardiac output (CO). We have now measured the CO (cardio-green technique of Arcilla and Rowe), mean arterial pressure (MAP) and heart rate (HR) in 45 new born mongrel puppies. The animals were divided into 3 groups:

I. ET (1.5 mg/kg IV) without DZ; II. DZ (600 μ g/kg IV) 20 min. prior to ET; III. (1200 μ g/kg IV) 20 min. prior to ET. MAP, CO and HR measurements (mean value $\pm$ SE, no. of animals given in parentheses) at 1 and 2 hours post Endotoxin.

Group	MAP			CO		
	Pre ET	1 Hr	2 Hr	Pre ET	1 Hr	2 Hr
I	53 $\pm$ 2 (15)	53 $\pm$ 2 (15)	27 $\pm$ 2 (14)	.37 $\pm$.03	.19 $\pm$.03	.12 $\pm$.01
II	53 $\pm$ 4 (9)	39 $\pm$ 2 (14)	30 $\pm$ 3 (14)	.39 $\pm$.04	.22 $\pm$.03	.19 $\pm$.03
III	45 $\pm$ 2 (8)	35 $\pm$ 3 (10)	19 $\pm$ 3 (10)	.34 $\pm$.03	.17 $\pm$.02	.13 $\pm$.02

There was no significant effect of ET or DZ (either dose) on HR. Although ET significantly ($P < .05$) decreased CO (Pre vs. post ET). DZ pretreatment produced no significant CO changes. However, MAP was significantly affected by DZ (DZ pretreatment vs ET alone). These results suggest that in newborn puppies ET shock, DZ causes early hypotension w/o affecting CO.

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FEEDING INTOLERANCE FOLLOWING THE OPHTHALMOLOGIC EXAMINATION OF NEONATES. Marcus C. Hermansen, L. Susan Sullivan, [Spon by MD Cunningham], Dept of Peds, Univ of Kentucky, Lexington.

Reports of isolated cases of necrotizing enterocolitis (NEC) following mydriatic administration and ophthalmologic examination prompted a comparison of the incidence of feeding difficulties 24 hours prior to (pre-exam) and 24 hours following (post-exam) the ophthalmologic examination of 51 newborns. All 51 infants had received 3 doses of 0.5% cyclopentolate and 2.5% phenylephrine drops prior to examination. The following data were obtained on critical review of the nursing notes:

N=51	Abdominal Distention	Vomiting	Bloody Stools	Gastric Aspirates	Loose Stools
Pre-Exam	3	6	1	4	3
Post-Exam	9	8	5	12	6

McNemar's Test (p) $< .05$ $> .1$ $> .1$ $< .025$ $> .1$
Sixteen infants (31%) had one or more symptom of feeding intolerance prior to the examination and 28 (55%) had symptomatology after the examination ($p < .005$). More abdominal x-rays were obtained (3 pre-exam, 9 post-exam) and more feedings were temporarily discontinued (1 pre-exam, 6 post-exam) following the examination. One infant had feeding intolerance 2 hours after examination and developed NEC during the 24 hour post-exam period. This study demonstrates the risks of feeding intolerance following the ophthalmologic examination of neonates. These risks may be due to known side-effects of mydriatics (cyclopentolate: atropine-like effects; phenylephrine: increased blood pressure), to the physical stress of the examination, or to a combination of both.