392 GLUCAGON TRIAL FOR PIGLET VERAPAMIL TOXICITY David McKinley, Arno Zaritsky (Spon by Glenn C. Rosenquist) GW Univ and Child Hosp Nat Med Cntr, Wash., D.C. and Univ of North Carolina, Chapel Hill, Dept of Ped.

Newborn swine have an increased sensitivity to verapamil induced cardiac depression. This connelates with the profound hypotension induced by verapamil in some infants. Glucagon has positive inotropic and chronotropic actions and affects cellular calcium channels. Therefore, glucagon's ability to reverse verapamil-induced hypotension in newborn swine was investigated.

Fourteen piglets (<24 hrs old, mean wt 1.5 kg) had aortic catheters placed one day prior to study. Mean Aortic Pressure (MAP) was measured continuously during the study. Ionized calcium levels were drawn on all animals and then a bolus infusion of 300 ug/kg of verapamil was administered. Five control animals received no further therapy. Nine animals were given 1 mg glucagon boluses one minute following verapamil.

Ionized calcium was 4.9 mg% or greater prior to the study (nl = 4.1-5.1) in all animals. Verapamil induced hypotension in both groups. The average MAP fell from 66 to 56 mm Hg (17%) in the treatment group and from 70 to 61 (13%) the control. Heart rate (HR) also slowed both in the treatment group from a mean of 220 to 200 and in the controls from 200 to 180. Glucagon failed to reverse the hypotension in the nine treated animals (MAP 54 Treated, 63 Control). HR did not return to baseline (HR 190 Treated, 180 Control). Neither difference was statistically significant by analysis of convariance.

Glucagon's cardiac effects peak at five minutes and the 1 mg dose fully saturates its receptors. Thus glucagon apparently lacks antagonism in the newborn swine for verapamil induced hypotension.

●393 MATURATION OF FUROSEMIDE PHARMACOKINETICS AND PHARMACODYNAMICS IN THE PIGLET. Jeffrey J. Miceli, Paul A. Kramer, Dennis J. Chapron, Mark H. Mirochnick, Ted S. Rosenkrantz and John R. Raye, School of Pharmacy & Dept. of Peds., Univ. of Ct, Storrs and Farmington, CT.

We have previously demonstrated an apparent decrease in renal tubular secretion and an increase in plasma half-life for furosemide (F) in VLBW infants. To pharmacokinetically characterize maturation of furosemide's tubular secretory pathway(s) and investigate whether pharmacodynamic effects such as sodium excretion undergo similar developmental changes, 3 and 18 day old piglets were administered a) an i.v. bolus dose or b) a primed continuous i.v. infusion of F, with quantitative fluid replacement. Plasma and urinary sodium and F levels, urine output and GFR were measured. Intrinsic secretory clearance of unbound F was calculated as were dose-response curves expressed as sodium excretion rate vs. log furosemide excretion rate. Mean intrinsic secretory clearance was significantly lower in the younger age group (51.7 vs. 104 ml/min/kg, $p<0.01$). While basal responses and slopes of the dose-response curves did not differ significantly, maximal response was increased in the older piglets (0.63 vs. 1.18 m mole Na/min, $p<0.05$). The F excretion rate required to stimulate a half-maximal response. however, was lower in the younger animals (0.06 vs. 0.15 μmoles F/min, $p<0.01$) and indicated an increased sensitivity to the drug. Thus the net response to F is a balance of maturational factors which influence both drug delivery and tubular responsiveness.

●394 FUROSEMIDE PHARMACODYNAMICS FOLLOWING ACUTE & CHRONIC ADMINISTRATION. Mark H. Mirochnick, Jeffrey J. Miceli, Dennis J. Chapron, Paul A. Kramer & John R. Raye, BU Dept. Peds., Boston MA & Univ. of CT Dept. Peds. & School of Pharmacy, Farmington, CT.

Furosemide (F) pharmacodynamics in VLBW infants have not been described following initial and subsequent doses during chronic adminstration. F acts from the luminal side of the loop of Henle and there is a log dose-response relationship between diuretic responses (Na excretion rate, urine output) and F urinary excretion rate. Serial urine collections were performed on 8 VLBW infants begun on F for treatment of BPD. Urine volume and F and sodium concentrations were measured. A linear relationship between diuretic response and F excretion rate was noted in all patients. Natriuretic response (mEq/hr) to initial doses of F decreased significantly with increasing gestational age ($p<.02$). The F excretion rate required to produce a standard diuretic response was significantly greater ($p=.05$) during chronic administration than following the initial dose. No consistent pattern of maturation of diuretic response was noted during subsequent chronic administration. We conclude that apparent sensitivity to F decreases with increasing gestational age at the start of therapy and with subsequent chronic doses. These changes may reflect the ability of the renal tubule to compensate for diuretic induced sodium and water loss. Results of previous studies of furosemide pharmacodynamics in VLBW infants following single initial doses can not be extrapolated to chronic administration.

●395 NEONATAL DIRECT HYBERBILIRUBINEMIA (DHB) ASSOCIATED WITH CHLORAL HYDRATE (CH) DOSAGE. John Muraskas, George H. Lambert, Ofelia Ayuste, Craig L. Anderson. (Spon. A. Cutilletta). Loyola U., Stritch School of Med., Dept. of Ped., Div. of Neonatology, Maywood, IL.

In order to investigate an apparent increase in the number of NICU newborns (NBs) with unexplained DHB, a retrospective analysis of all NBs admitted to the NICU over an 18 month period was conducted. The study revealed 11 newborns with undiagnosed DHB defined as direct bilirubin ≥ 2 mg/dl or ≥ 10% of the total bilirubin level. Four of the 11 NBs had identifiable factors which are known to cause DHB. Two of the 4 NBs had severe perinatal asphyxia with elevated liver enzymes and 2 NBs had prolonged hyperalimentation due to gastrointestinal adnormalities. All of the remaining 7 NBs (Group 1) did not have a diagnosable nor identifiable cause, but all had received CH 30-40 mg/kg q 4-6 h for sedation while on the ventilator. In these NBs, the DHB began to decrease within 2 days of the last CH dose. We next reviewed all charts of NBs who had received more than one dose of CH for sedation and did not have DHB (Group 2). The table compares these two groups including the total CH dose/kg received.

Group	DHB	N	Gest Age (±1SD)	Total CH dose
1	+	7	30±7wks	2404 ± 2362 mg/kg*
2	-	37	32±4wks	631 ± 1620 mg/kg

*$P<0.05$ vs Group 2

In summary, prolonged administration of CH appears to be associated with DHB in NBs in a dose response and temporal manner. Similar CH-induced hepatic toxicities have been reported in adults and animals. The human NB may be more sensitive to CH due to decreased metabolic clearance of CH and its active metabolite.

●396 TRANSCUTANEOUS SAMPLING OF THEOPHYLLINE AND CAFFEINE IN PRETERM INFANTS. M. Gail Murphy, Carl C. Peck, Dale P. Conner, Brenda J. Bolden, Laura Fox, Donna Rodden, Gerald B. Merenstein Uniformed Services Univ., Beth., Md. Univ. of Co., Denver, Co. (spon. by Itzhak Brook)

The feasibility of noninvasive sampling of theophylline (TH) and caffeine (CF) into a novel Transdermal Collection System (TCS) has been studied in 14 preterm infants (PI) on 1-3 occasions. The TCS induces the outward migration of drugs by juxtaposing 2.54 cm2 of skin with a transfer medium (saline aquagel), containing a binding sink (activated charcoal). 14 PI (25-34 weeks gestation and 3-175 days old) who were receiving TH therapy had 4 TCS's placed on the back for 12 hours during which one or more routine plasma concentrations (Cp) were measured. Cp and the flux of TH ((50-1850 ng) and CF ((50--200 ng) into each TCS were determined by HPLC. Apparent permeability coefficients (Kp) = (TCS-flux (ng/cm2/hr)/aveCp during TCS placement) of any one PI showed little change over time once the PI was)2 wks old. Our Kp for CF ranged from .2-6*10^-3 cm/hr and our Kp for TH (.2-8*10^-3 cm/hr) overlap the range (.8-1.4*10^-3 cm/hr)derived from a report of transdermal delivery of TH in PI by Evans(JPEDS 107:307.1985). We have shown that transcutaneous sampling of TH and CF in PI is feasible and speculate that development of this technology may provide a powerful new tool for noninvasively sampling TH or CF therapy in Pi.

397 DEVELOPMENTAL ASPECTS OF PHENOBARBITAL DOSAGE REQUIREMENTS IN NEWBORN INFANTS FOR SEIZURE CONTROL. Milap Nahata, Tami Masuoka, Robert Edwards, Colleges of Pharmacy and Medicine, The Ohio State University and Children's Hospital, Department of Pediatrics, Columbus.

Phenobarbital (PB) is the most widely used drug to control seizures but specific dosage guidelines are not available in infants of varying gestational ages (GA). The primary objective of this study was to develop the dosage guidelines in newborn infants relative to age to control seizures. Fifty-one patients (27 premature infants: GA 27-38 weeks; 24 term infants) receiving PB, 3-6 mg/kg/d were studied during the first month after birth. Multiple serum concentrations were determined in each patient during extended therapy. Trough serum concentration of PB ranged from 12.5-50.2 μg/ml. PB serum concentrations were within therapeutic range (15-40 μg/ml) in 99 of 114 cases at the maintenance dose of 3.5-4.5 mg/kg/d. The remaining 15 cases were above 35 weeks of GA and required PB doses of 5 mg/kg/d to control seizures. These data suggest that the maintenance dose of PB during the first month after birth should be 3.5-4.5 mg/kg/d in infants < 35 weeks and 4.0-5.0 mg/kg/d in those > 35 weeks GA. Term infants with asphyxia had higher trough serum concentration than those with asphyxia. In six infants, trough serum concentration decreased by 30-50 percent at the same dose during a three weeks period. This suggests that PB serum concentration should be monitored frequently during the developmental period.