**391** GENTAMICIN THERAPY IN PREMATURE NEONATES: DOSAGE INTERVAL (DI) BASED ON GESTATIONAL AGE (GA). Eduardo J. Lugo, Franklin R. Smith and James S. Rawlings. (Spon. by James W. Bass). Tripler Army Medical Center, Department of Pediatrics, Honolulu, HI.

Peak gentamicin serum concentrations (GSC) of 4-12 mcg/ml and trough concentrations < 2 mcg/ml are recommended for effective therapy without toxicity. Currently recommended gentamicin dosage regimens for premature neonates within the first week of life have a significant incidence of toxic or subtherapeutic GSC. In a previous study by the authors using a standard regimen with fixed DI, an inverse linear correlation was found between peak and trough GSC and GA. A new gentamicin dosage regimen was formulated based on this correlation using a one-compartment pharmacokinetic model. This regimen consists of a 3.5 mg/kg dose given at a DI which is inversely related to GA: DI = 50.5 - 0.76 GA. This regimen is designed to yield peak and trough GSC of 8.0 mcg/ml and 1.5 mcg/ml, respectively, in premature infants, irrespective of GA. To test this new regimen, 32 premature neonates were studied within the first week of life. Mean GA was 31.4 weeks (range 25-36); mean birth weight was 1675 grams (range 570-2900). Mean peak and trough GSC (± SD) were 7.0 ± 1.17 mcg/ml and 1.1 ± 0.26 mcg/ml, respectively. All GSC were within the recommended range. This is the lowest incidence of inappropriate GSC in any series reported in the literature. Serial peak and trough GSC did not vary significantly in individual patients during the first 4 days of therapy. The previously observed correlation between GSC and GA was lost with this regimen. We conclude that relating DI to GA in this fashion is a simple and effective way of achieving optimal peak and trough GSC in premature infants of various GAs.

**392** VITAMIN PREPARATIONS IN NEONATAL PARENTERAL NUTRITION (PN) Mhairi G. MacDonald, Anne B. Fletcher, Marilea K. Miller, Roger Boeckx, Pamela R. Getson, (Spon. by G.B. Avery) George Washington Univ. Children's Hosp. Nat. Med. Ctr., Neo. Div., Washington, D.C.

Toxicity to neonates from drug solvents is of concern. We reported serum hyperosmolarity due to Propylene Glycol (PG) in MVI-12. This study compared two groups of infants weighing <1500 grams. Gr PG-received MVI-Conc. (with PG) 1 cc/d in their PN and Vit. E 50 u/wk IM. Gr Mann.-received MVI-Ped. (with Mannitol) 6.5 cc/d. Serum & urine osm. PG levels, BUN, creatinine, Na & glucose were measured days 0,2,5,12,19,26,33 & 40 on PN. Weight, urine output, and fluid intake were measured daily. Vit E levels were measured on days 5,26 & 33 on Pn. Mannitol levels were not measured. RESULTS: There were no differences between the groups in birth weight, gest. age, sex or age & wt. at start of PN. PG <1000gm-serum mosm. correlated with serum PG during first 12 days of PN. (PG levels 2.4-108.4 mg/dl.) 14.2% of serum osmol. values were> 310mosmol/L. Mann. gr.< 1000gm-12.6% serum mosm. were> 310mosmol/L. No diuretic effect of Mannitol was detected. MVI-Ped. in recommended doses may produce higher than desirable vit. E levels.

| PG group (n=30) | | | Mannitol group (n=17) | | |
|---|---|---|---|---|---|
| Day | Range Vit. E (ugm/ml) | Mean Vit.E | Day | Range Vit.E (ugm/ml) | Mean Vit.E |
| 5 | 9.3-38.5 | 20.5 | 5 | 16.0-43.5 | 27.3 |
| 26 | 10.9-28.9 | 20.3 | 26 | 17.4-53.3 | 37.4 |
| 33 | 8.7-33 | 23.4 | 33 | 19.6-66.7 | 43.3 |

**393** THE EFFECT OF NALTREXONE ON APNEA OF PREMATURITY & SERUM B-ENDORPHIN LEVELS. Mhairi G. MacDonald, Georgis G. Kefale, Immanuella R. Moss, Robert J. Fink, Harold M. Ginzburg, Lin Chin, James H. Davis. (Spon. by G. B. Avery). George Washington Univ., Children's Hospital National Medical Center, Neonatology Division, Washington, D.C.

Naltrexone is a long-acting analogue of Naloxone with 17x greater opiate antagonist activity. (Time to peak, post i.v. admin. = 1-2h.T1/2=10h in adults). Animal studies, and one study in prematures, suggest that opioid antagonists reverse apnea of prematurity via antagonism of B-endorphins (B-ED). Our study infants weighed <1,700 gms (Gest. age (GA) 28-35 wks) & had significant apnea. (Min. 10/day. Duration 15 sec and/or HR <100 /min and/or cyanosis). 5 infants had not received methylxanthinés (Group A). 11 infants were receiving methylxanthines (Gr. B). EKG, chest wall movement, nasal airflow, TcP02 & TcPC02 were monitored for 4-6h pre-Naltrexone. Naltrexone 1-3 mgm/k was given i.v. & monitoring continued for 4-6h. Samples for B-ED assay were taken prior to & 1h post-Naltrexone, & also from 10 control infants weighing <1,700 gms, without apnea or other significant pathology (GA 28-35 wks). RESULTS: No drug side-effects were detected. Gr. A- No infant showed an improvement in apnea post-Naltrexone. Gr. B- 5 recordings were unsatisfactory. 3 infants showed no change & 3 infants showed more severe apnea post-Naltrexone. No significant difference was found in serum B-endorphin levels before & after Naltrexone. B-endorphin levels were significantly higher (p <.001) in infants with apnea of prematurity than in control infants. B-endorphin levels did not change with increasing gestational or postnatal age.

† **394** INCREASED CLEARANCE OF PHENYTOIN (PH) IN PREGNANCY IS DUE TO MATERNAL, NOT FETAL OR PLACENTAL, METABOLISM. David Manchester, Curt Freed, Peter Hulac and Peter Earl. University of Colorado School of Medicine, University Hospital, Departments of Pediatrics and Medicine, Denver, 80262.

Clearance of Phenytoin (PH) increases during pregnancy (Lander et al. Eur. J. Clin. Pharm. 1984), but the sites of its apparently enhanced metabolism and the mechanisms responsible are unknown. We have observed decreased maternal clearance of PH within a few hours of delivery suggesting that products of conception either participate directly in metabolism of PH or stimulate maternal systems. To approach this problem, we estimated fetal contributions to PH metabolism by following disappearance of transplacentally acquired drug in 9 neonates born to women whose PH requirements had increased during pregnancy and compared in vitro metabolism of PH by placentas from treated (N=2) and non-treated (N=5) women with that of rat hepatic microsomes. In the first 18 to 24 hours following delivery, plasma PH levels decreased by only 10-50% in non-breast fed neonates indicating that increased clearance of drug during pregnancy could not be accounted for by fetal metabolism. While oxidation of PH was detectable in reaction mixtures incubated for 30 to 60 min with rat liver microsomes, no metabolites could be detected following incubations up to 14 hours with either placental homogenates or postmitochondrial supernatants. These results suggest that products of conception do not participate significantly in PH metabolites during pregnancy. Rather it appears that a factor(s) produced by the fetal-placental unit directly stimulates maternal metabolic pathways.

**395** HEMODYNAMIC CONSEQUENCES OF NITROGLYCERIN INFUSION DURING GROUP B STREPTOCOCCAL SEPSIS IN PIGLETS. William L. Meadow, Brian F. Rudinsky, and Elene Strates (Spon. by K.S. Lee). Dept. of Pediatrics, Univ. of Chicago Medical Center, Chicago, IL

Cardiovascular collapse is a common cause of death in newborn sepsis. Vasodilator therapy has recently been suggested to be of significant hemodynamic benefit in a number of shock states. We assessed the effects of nitroglycerin (NG), a direct-acting smooth muscle relaxant, on systemic and pulmonary hemodynamics in a piglet model of Group B Streptococcal sepsis.

Piglets (n=4) were anaesthetized, intubated, and ventilated. Systemic blood pressure (BP), pulmonary artery pressure (PAP), cardiac output (CO), and heart rate (HR) were monitored directly and continuously. Sepsis was induced by continuous infusion of serotype Ib Group B Streptococci (GBS) @ approximately 5 X $10^7$ organisms/kg/min. Ventricular filling pressures were held constant during the entire experiment by adjustment of i.v. infusion rate.

After 30 minutes of GBS infusion, CO fell by 32 ± 7% (S.D.), PAP rose by 225 ± 97% (both p< 0.01) while BP fell by 1 ± 6% and HR rose b 4 ± 4% (both p = N.S.) While GBS infusion continued, NG infusion was begun. For NG @ 8 mcg/kg/min and 16 mcg/kg/min respectively, CO fell by 7 ± 9% (p = N.S.) and 19 ± 11% (p< 0.01), BP fell by 9 ± 6% (p< 0.05) and 13 ± 4% (p< 0.01), PAP rose by 2 ± 9% and 4 ± 16% (both p = N.S.), and HR rose by 7 ± 9% (p = N.S.) and 11 ± 6% (p< 0.05).

Conclusion: NG infusion during GBS sepsis in piglets had little apparent hemodynamic benefit.

**396** SELECTIVE SYSTEMIC VASOCONSTRICTION WITH PRESERVED CARDIAC OUTPUT DURING GBS-INDUCED PULMONARY HYPERTENSION IN PIGLETS: AN ALTERNATIVE APPROACH TO PPHN? William L. Meadow, Brian F. Rudinsky, and Elene Strates (Spon. by K.S. Lee). Dept. of Peds, U. of Chicago Med Center, Chicago, IL

Pharmacologic therapy directed at selectively lowering pulmonary artery pressure (PAP) in persistent pulmonary hypertension of the newborn (PPHN) has been largely unsuccessful. As an alternative approach, we have modelled PPHN in septic piglets, and achieved selective elevation of systemic blood pressure (BP) while preserving cardiac output (CO).

Piglets (n=4) were anaesthetized, intubated, and ventilated. BP, PAP, and CO were measured directly and continuously. Pulmonary hypertension was induced by intravenous infusion of serotype Ib Group B Streptococci (GBS) @ approximately 5 X $10^7$ organisms/kg/min.

After 30 minutes of GBS infusion, PAP had risen by 225 ± 97% (S.D.), CO fell by 32 ± 7%, (both p< 0.01) and BP fell by 1 ± 6% (p = N.S.). While GBS continued, infusions of Nitroglycerin (NG) @ 16 mcg/kg/min plús Epinephrine (EPI) @ 2 mcg/kg/min were begun. After 1 hour of NG + EPI, BP had risen by 41 ± 18% (p< 0.01), while PAP fell by 3 ± 18% and CO fell by 18 ± 24% (both p = N.S.).

Conclusions: 1) PPHN can be modelled by GBS infusion in piglets. 2) NG + EPI selectively elevated BP without raising PAP in this model. 3) NG + EPI induced selective elevation of systemic BP without significantly decreasing CO. 4) Selective systemic vasoconstriction with preserved CO may be a feasible strategy for human infants with PPHN.