343 BETA-ADRENERGIC RECEPTORS (BAR) AND CYCLIC AMP (cAMP): TERM WHITE CELLS ARE MATURE, PRETERM ARE NOT. David A. Auerbach (Spon. by Jane E. Brazy) Duke University, Department of Pediatrics, Durham, North Carolina

To test the hypothesis that direct measurement of adrenergic maturity in newborns is possible by measuring cord blood white cell BAR and hormone stimulated cAMP, heparinized cord blood obtained at term (T) and at 29-30 weeks (PT) was compared with adult (A) controls. Polymorphonuclear leukocytes (PM) and mixed monocytes-lymphocytes (ML) were separated and counted. Intact viable cells were used in radioligand-receptor binding assays with ^{125}I-iodocyanopindolol (CYP) to determine BAR density (sites /cell), affinity and specificity. Intracellular cAMP (pmol/ 10^6 cells/ 5 min) in control and 10μM isoproterenol (ISO) exposed cells was assayed by radioimmunoassay. CYP binding to one class of high affinity sites with beta$_2$ specificity was reversible and saturable with similar affinities in all groups. PM from T and A had similar BAR densities (mean ± s.e.m. N=5) 2039 ± 252 and 2045 ± 344, which were greater than PT (N=3) 907 ± 230. BAR densities on ML from T and A, 1289 ± 203 and 1069 ± 259 were greater than PT 538 ± 125. Net ISO stimulated cAMP was similar in ML from A and T, 7.2 ± 1.2 and 7.5 ± 1.5, but less in PT 3.7 ± 0.9. Net ISO stimulated cAMP in PM from A,T, and PT were similar, .59 ± .14, .76 ± .16 and .94 ± .1. Although ML had fewer BAR than PM they had higher basal and ISO stimulated cAMP levels.

These studies demonstrate that at term, PM and ML possess the same BAR and cAMP characteristics as adult cells but PM and ML at 30 weeks have fewer BAR. CAMP response is similar throughout gestation in PM but is reduced in preterm ML.

344 MATERNAL AND FETAL CARDIOVASCULAR RESPONSES TO SINGLE DOSE DIAZEPAM ADMINISTRATION IN PREGNANT EWES.

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Fourteen experiments were conducted in seven chronically instrumented pregnant ewes equipped with electromagnetic flow probes around the main uterine arteries and with catheters inserted into maternal and fetal aorta and inferior vena cava. Following collection of baseline data, maternal observations were made at 15, 30, 45, 60, 90, 120, 150, and 180 minutes after a maternal intravenous bolus injection of Diazepam, 0.2 mg/kg, while fetal parameters were assessed 30, 90, and 150 minutes after drug infusion. Mean maternal pH decreased at 15 minutes ($p < 0.01$) associated with a reduction in mean maternal PO_2 ($p < 0.01$) and an increase in mean maternal PCO_2 ($p < 0.01$), which persisted for most of the observation period. Reduction in maternal PO_2 was not seen after 30 minutes until observed again at 150 and 180 minutes ($p < 0.01$). Maternal and fetal blood pressure, fetal heart rate and uterine blood flow remained unchanged. Mean fetal pH decreased at 30, 90 and 150 minutes ($p < 0.01$). Fetal PO_2 decreased at 150 minutes ($p < 0.01$). Conclusion: Single bolus Diazepam administration is associated with modest reduction in fetal pH and PO_2 without any changes in uterine blood flow. Changes in maternal respiratory physiology and/or a direct fetal effect may be responsible for these observations.

● 345 MECHANISMS OF ACTION OF DOXAPRAM IN NEONATAL APNEA. Keith Barrington, Neil Finer, Kathrine Peters University of Alberta, Royal Alexandra Hospital, Department of Neonatology, Edmonton, Alberta, CANADA

Doxapram (Dx), a central respiratory stimulant has been reported to reduce neonatal apnea. To further assess the action and efficacy of Dx, we studied 8 infants with apnea refractory to Aminophylline at serum levels of 50 - 108 umol/l. Airway occlusions and measures of minute ventilation were performed 1 hr prior and 3 & 24 hr following Dx at a dose of 2.5 mg/kg/hr IV. No loading dose was given. Apnea frequency and duration as determined by continuous cardiorespirography, decreased within 6 hr. Minute ventilation increased, due to an increase in Vt, within 3 hr of Dx infusion, the increase in Ve becoming statistically significant by 24 hr. No changes in Ti, Te or Ttot were observed. PO.1 and Vt/Ti were significantly increased following 24 hr of Dx therapy.

	PO.1 cm H_2O	VE ml/kg/min	VT ml/kg	Vt/Ti ml/kg/sec	Apnea/hr
PRE	2.5	339	5.3	14.5	1.17
24 HR	4.4	503	7.4	20.4	0.21
	p<.05	p<.05	NS	p<.05	p<.05

Six infants' blood pressure increased with Dx therapy, in one severely enough to necessitate stopping Dx. Dx increases ventilation and respiratory centre output similar to effects observed with aminophylline and caffeine, indicating that respiratory centre output can be further increased even in the presence of adequate levels of xanthines. The observed hypertension suggests that further studies are necessary before the routine usage of Dx in neonates.

● 346 VENTILATORY RESPONSE TO HYPOXIA AND HYPERCARBIA AFTER CAFFEINE INFUSION IN THE NEWBORN LAMB: CONTRIBUTION OF THE PERIPHERAL CHEMORECEPTORS. Pierre W. Blanchard, Aurore Coté, Steve Hobbs, Jacob V. Aranda, Michel A. Bureau. McGill University, Montreal Children's Hospital, Department of Pediatrics, Montreal, Québec, Canada.

Caffeine is a methylxanthine currently used in the prevention of disorders in the control of breathing in the pediatric age group. Despite this wide acceptance, the mechanisms implicated in the respiratory action of caffeine are still unclear. The current study has evaluated the effect of caffeine on O_2 and CO_2 drive of breathing. Seven awake, non-premedicated, non-intubated lambs (mean age 53h) were used for this study. Before and after caffeine therapy (10 mg/kg), progressive isocarbic hypoxia was used to assess the peripheral chemoreceptors, and hyperoxic rebreathing hypercapnea was used for the central receptors. The output of these chemoreceptors was measured by changes in minute ventilation (VE), mean inspiratory flow (Vt/Ti) and timing of respiration (Ti/Ttot). Mean plasma level of caffeine was 13.2 mg/L. Caffeine increased the ventilatory response to isocarbic hypoxia (FiO_2: 0.21 to 0.06); the difference was particularly significant with low FiO_2. At FiO_2= 0.06, VE was 915 before and 1213 ml/kg/min after caffeine ($p<0.02$); Vt/Ti was 30.9 before and 40.2 ml/kg/s after caffeine ($p<0.03$). No significant change was induced by caffeine infusion on the CO_2 response curve. We conclude that in the newborn lamb, caffeine potentiates the response of the peripheral chemoreceptors; no central effect of caffeine was observed in our study.

● 347 RATIONAL DOSING OF RANITIDINE (R) IN PEDIATRIC ULCER DISEASE (UD). Jeffrey L. Blumer, Michael D. Reed, Fred C. Rothstein, Carolyn M. Myers, and Cheryl A. O'Brien, Case Western Reserve University School of Medicine, Rainbow Babies & Childrens Hospital, Departments of Pediatrics and Pharmacology, Cleveland, Ohio 44106

Dosing requirements for R were determined in 12 children (C) aged 3.5-16 yrs with endoscopically proven UD. Gastric acid output (GA) was monitored continuously during the first 2 days of therapy. The therapeutic endpoint was suppression of GA by ≥90%. C received 0.06mg R/kg over 15 min plus an infusion of 0.02 mg R/kg/hr. Each hour they received a bolus of 0.004 mg R/kg and the infusion was increased by 0.02 mg/kg until the endpoint was reached. The infusion was then stopped and for 12 hrs blood, urine and gastric fluid were collected for the R and GA analysis. Values were used to calculate an IV dose which when given every 6 hr would suppress GA ≥90%. On Day 2 the dose was given and R pharmacokinetics (PK) and GA were repeated. When C were eating, the IV R was crossed over to oral R. Following repeat PK analysis the doses of R were individually adjusted to give a BID dose which would result in an average serum R concentration which suppressed GA ≥90% C were then discharged to receive that dose for 6 wks. A serum R concentration of 40-60 ng/ml resulted in the desired suppression of GA. PK analysis revealed (x±SD) $t_{1/2}$, 1.8(0.2)hr; Vd, 2.3(0.9) L/kg; Cls, 794.7(334.2) ml/min/1.73m^2. The absolute bioavailability of R averaged 48% (range 22-96%). Minimal PK differences were observed comparing IV and oral dosing. All ulcers were completely healed on repeat endoscopy. No C experienced any side effects.

348 PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF CIPROFLOXACIN (CIP) IN CYSTIC FIBROSIS (CF). Jeffrey L.Blumer, Robert C. Stern Carolyn C.Myers, Jeffrey D.Klinger, Michael D. Reed. Case Western Reserve University School of Medicine, Rainbow Babies & Childrens Hospital, Departments of Pediatrics & Pharmacology, Cleveland, Ohio 44106

We evaluated the comparative in vitro efficacy of CIP against CF sputum Pseudomonasisolates and its in vivo PK characteristics in CF patients compared with normals (NC). When evaluated in vitro against 10^4 and 10^7cfu/ml P.aeruginosa (PA) and P.cepacia (PC) CIP proved more potent than other antipseudomonal drugs tested. For PA MIC_{95} ranged from 0.5-1μg/ml and MBC_{95} was 1μg/ml; for PC the MIC_{95} and MBC_{95} ranged from 16-32μg/ml. Following a single 750 mg oral dose of CIP the PK in 6 CF and 6 age-and sex-matched NC were determined. In CF and NC the following PK parameters were determined (x±SD): CF-$t_{1/2}$,4.5±096 hr; Cl_s, 556.41±107.09 ml/min/1.73m^2; Vdss 195.35±51.92 L/kg; Cl_r, 352.8±144.64 ml/min/1.73^2; ka,3.6±1.62 hr^{-1}; NC-$t_{1/2}$ 4.80±.97 hr; Cl_s, 690.86±80.16 ml/min/1.73m^2; Vdss, 230.13±43.38 L/kg;Cl_r,349.65±162.01 ml/min/1.73m^2; ka, 1.14±.61 hr^{-1}. Only the Cl and ka were significantly different ($p < 0.01$) between CF and NC. Another group of 12 CF patients received 750 mg CIP orally on each of two occasions with or without prior pancreatic enzyme supplementation (PE). PE had no effect on $t_{1/2}$,Cl_s, Vdss, Cl_r, or ka. Sputum penetration of CIP was evaluated PE. The times to peak and peak CIP concentration in serum and sputum were 145 and 189 min and 4.22 and 3.00μg/ml respectively. PE had no significant effect on either parameter. The apparent sputum CIP $t_{1/2}$,4.34±1.44 hr was not significantly different from the serum $t_{1/2}$and the ratio of the sputum:serum AUC was 0.93±.52 suggesting excellent drug penetration. Our data suggests that CIP has both favorable PD and PK characteristics in CF. The PK are unaffected by exocrine pancreatic insufficiency. Thus, a clinical efficacy study in CF patients with acute pulmonary exacerbations appears warranted.