† 355 EFFECTS OF INTRAVENOUS DILTIAZEM ON HEMODYNAMICS AND REGIONAL BLOOD FLOWS IN THE NEWBORN PIGLET. Martine Clozel, Jean-Michel Hascoet, Jean-Paul Clozel, Pierre Monin, Paul Vert. INSERM U 272, Nancy, France.

Calcium antagonists are a new class of drugs which may be useful during the neonatal period. Since their effects on regional blood flows (RBF) had not been studied, we assessed the effects of IV diltiazem (DTZ) on hemodynamics and RBF measured with radioactive microspheres in urethan- anesthetized piglets (age = 5.4 ± 0.6 d). Six piglets received DTZ (0.5 and 1 mg/kg, leading to plasma concentrations of 0.52 ± 0.03 and 1.14 ± 0.07 ug/ml respectively, as measured by high pressure liquid chromatography). Six other piglets received saline (control group). All the parameters studied were stable in the control group. With both doses, DTZ decreased mean arterial blood pressure (28 and 24%, $p < 0.001$) and heart rate (9 and 13%), $p < 0.001$). Cardiac index and systemic vascular resistance were not modified. DTZ markedly increased the coronary blood flow (54% and 55% after 0.5 and 1 mg/kg respectively, $p < 0.01$) with no change in the endocardium/epicardium ratio. Coronary resistance was decreased. To a lesser extent, DTZ (0.5 mg/kg) increased significantly ($p < 0.05$) the blood flow to the brain (27%), liver (7%), ileum (6%) and diaphragm (26%). In contrast, DTZ at a dose of 1 mg/kg induced a significant decrease in renal blood flow (37%, $p < 0.05$). We conclude that in the newborn piglet, blockade of the slow calcium channels by DTZ induces a coronary vasodilatation. The decrease in renal blood flow after high doses requires further investigation.

356 SERUM NETILMICIN LEVELS IN PREMATURE INFANTS. Leandro Cordero, Larry Arwood, Susan DiCenzo, James Visconti. OSU College of Medicine, Department of Pediatrics (Spon. by Dwight A. Powell).

Aminoglycosides can be safely used by close monitoring of serum concentrations. Limited information and the unique physiology of prematures during the first week of life makes interpretation of peak and trough levels more difficult. This study was designed to measure serum netilmicin levels following a 2.5 mg/kg push IV infusion. Blood samples were taken on the fifth day of therapy (age) one hour before and one, six and eleven hours following a dose. Fifteen prematures weighing 1000-1500 gms at birth and 20 others whose weight ranged from 1501-2750 gms comprised the study population. All prematures were AGA and of them, only 2 were severely asphyxiated. At the time of the study, 10 neonates were still on respirators. Serum and urine sodium and creatinines, BUN and urinalysis were obtained in 28 of these infants. No evidence of renal dysfunction was found. All infants received 100 mg/kg IV ampicillin every 12 hours but none were being treated with diuretics. Serum netilmicin levels were measured by an enzymatic immunoassay (SYVA), peak and trough were calculated by extrapolating the first order decay curve. Peak levels ranged from 3.4 to 14.4 mcg/ml ($\bar{x}$ 6.6 ± 2.5mcg/ml SD) and 80% of them were above 4 mcg/ml. Half of the small prematures (1000-1500 gm Bwgt) presented trough values above 3mcg/ml. Pharmacokinetic analysis of our data predicts that a 2.5 mg/kg loading dose followed by 2 mg/kg given every 12 hours will decrease by one-half the number of small prematures exceeding the considered "safe" trough level (>3 mcg/ml).

357 TOLAZOLINE INHIBITION OF PLATELET AGGREGATION. James T. Courtney, Kathy A. Kenal, and Joseph A. Garcia-Prats, (Spon. by Thomas N. Hansen), Baylor College of Medicine, Department of Pediatrics, Houston, Tx.

Tolazoline (TZ), an imidazoline compound with vasodilatory and histaminic properties, is used in the therapy of neonatal persistent pulmonary hypertension (PPH). Inhibition of thromboxane A2 (TBX-A) synthesis by TZ has been reported. The in-vitro effects of TZ on platelet aggregation were studied. Platelet rich plasma obtained from 6 healthy adults and from cord blood samples of 6 healthy term infants was incubated with TZ and aggregated with ADP (10μM). At increasing concentrations of TZ, decreases in maximal aggregation occurred, followed by disaggregation (mean±SEM):

	Maximal Aggregation (%)				10-Minute Aggregation (%)			
TZ-μg/ml	0	100	500	1000	0	100	500	1000
Adults	80±4	70±4	54±6†	35±4†	80±4	65±9	41±7†	12±4†
Newborns	81±3	76±3	65±7	34±3†	77±2	73±3	52±9	2±1†

† significant decrease from control ($p<.01$)

The relationship between TZ concentration and both maximal and 10-minute aggregation was linear up to 10^3 μg/ml ($r \geq 0.88$). The inhibition of primary aggregation at the highest TZ concentrations is inconsistent with TBX-A inhibition alone. Preliminary data, using a radioimmunoassay, suggest an increase in platelet cyclic AMP when incubated with TZ, perhaps mediated by histamine receptors. In-vivo inhibition of platelet aggregation and TBX-A release by TZ may be benefical in some forms of PPH.

† 358 THE ACTIVITY OF ACETAMINOPHEN AND ITS STRUCTURAL ANALOGUES ON IN VITRO PROSTAGLANDIN SYNTHESIS FROM THE DUCTUS ARTERIOSUS OF THE SHEEP FETUS. Marthe Dalpé-Scott and Robert G. Peterson. University of Ottawa, Departments of Pharmacology and Pediatrics, Ottawa, Ontario, Canada.

We have previously shown that A4AP has the same activity as acetylsalicylic acid (ASA) in producing constriction of the ductus arteriosus (DA) in the chronically catheterized sheep fetus. We report here that PGI_2 synthesis by fetal lamb DA homogenates is inhibited by A4AP concentrations similar to levels achieved in the fetus. The K_I was lower than that obtained for brain homogenates (Table). Analogues of A4AP synthesized in this laboratory: N-Acetyl-3-AminoPhenol (A3AP) and N-Acetyl-2-AminoPhenol (A2AP), differ from A4AP in that A3AP cannot be oxidized whereas A4AP and A2AP oxidize readily to reactive intermediates. A4AP and A2AP were as effective as ASA to inhibit PGI_2 synthesis in the DA whereas A3AP was 25 to 50 times less effective. The ability of prostaglandin synthetase to oxidize A4AP has been demonstrated. We conclude from these studies that the mechanism whereby A4AP is an inhibitor of prostaglandin synthesis is via a metabolic oxidation similar to that which can lead to hepatic injury.

K_I's for 50% inhibition of PGE_2 synthesis (brain) or 6-keto $PGF_{1\alpha}$ (DA)

Drug	Brain	Ductus	
	uM	uM	ug/ml
A4AP	75	10	1.5
A3AP	250	250	38
A2AP	25	5	0.7
ASA	50	10	3.0

359 NEONATAL APNEA AND MATERNAL CODEINE USE. Jonathan M. Davis and Vinod K. Bhutani. (Spon: Alfred M. Bongiovanni). Univ. of Pa. Sch. of Med., Pennsylvania Hospital, Section on Newborn Pediatrics, Philadelphia.

The occurrence of apnea in term and near term neonates is usually associated with a definitive organic etiology. We have recently studied 4 infants ($\bar{x}$ GA=37 wks, range 35-40 wks; $\bar{x}$ BW= 2660g, range 1980-3140g) with significant apnea and increased periodic breathing. All infants had been born by cesarean section (apgars 8/9) following uncomplicated perinatal courses and were well until 4-6 days of age when apnea developed. Complete bacteriologic, hematologic, metabolic, and cardiac evaluations were normal. Cardiorespirograms were abnormal showing multiple episodes of short apnea (5-10 sec $\bar{x}$=25.5, range 15-39; 10-15 secs $\bar{x}$=23, range 10-35) and increased periodic breathing ($\bar{x}$=16.3%, range 1-35%). One episode of prolonged apnea (>20 secs) and multiple bradycardias were seen in one patient.

All mothers had been breast feeding and receiving codeine 60 mg every 4-6 hours for analgesia. Breast feeding was held for 24 hours and the codeine discontinued. Codeine was not detected in the serum of one infant. Apnea resolved within 24-48 hours and the infants were discharged. Repeat cardiorespirograms within 7-10 days were normal. Experience in these 4 infants suggest: 1)Although only trace amounts of codeine are reported to enter breast milk, it may be sufficient to affect newborn respiratory control. 2)The metabolism of codeine in the newborn is uncertain. It may take 4-5 days for sufficient drug to accumulate and influence respiratory control. 3)Caution should be used with codeine administration in breast feeding mothers.

360 CARDIAC DEPRESSANT EFFECTS OF PROSTAGLANDIN D_2 (PGD_2) IN AWAKE LAMBS 2 TO 32 DAYS OLD. Willa H. Drummond, Hugh H. Shrager, Wendy A. Dailey, S. Lee Evans. University of Florida College of Medicine, Gainesville.

Cardiac and systemic pressor effects of PGD_2 are variable in previous reports utilizing animals pretreated with pentobarbital paralysis and indomethacin. To test PGD_2 effects without other drugs, 16 lambs were operated at <24 hours to ligate the ductus arteriosis and to place catheters in the aorta, pulmonary artery (PA), left atrium (LA) and inferior vena cava (IVC) and a flow transducer around the main PA. Vascular and cardiac effects of PGD_2 at 0.1, 1, and 10 ug/kg x 1 min on aortic (SAP), PA and LA pressure (PAP, LAP), cardiac output (CO), heart rate (HR) and systemic and pulmonary vascular resistance (SVR, PVR) were studied during normoxia (N) and hypoxia (H) at ages 2.5, 11.4 and 25.5 days. PGD_2 had age and oxygen related pulmonary vasodepressor effects. SAP and SVR increased from 5 to 20 mmHg ($p<.05$-$.0001$) at all doses and ages, under both N and H. HR and cardiac output fell at all doses. At 10 ug/kg/min:

	Δ HR beats/min		Δ QP ml/kg/min		Δ LAP mmHg	
Age	(N)	(H)	(N)	(H)	(N)	(H)
2.5	-51±9*	-59±14*	-24±5*	-35±12*	2.3±.7*	2.3±.4*
11.4	-36±10*	-85±9*	-11±8	-30±11*	1.7±.5*	2.0±.5*
25.5	-38±7*	-47±12*	-21±5*	-16±6*	1.3±.4*	0.7±.4

(*p<.05-0001)

PGD_2 in intact unanesthetized lambs is a moderate systemic pressor and depresses cardiac function, perhaps reflexly. Neither age nor hypoxemia alters the response, unlike pulmonary vascular changes. Thus, interactions of PGD_2 with other drugs alter cardiac and systemic circulatory resonses. Ill infants treated with combinations of barbiturates, indomethacin and/or paralytic agents may exhibit quite variable responses if also treated with PGD_2.