● 361 THE USE OF CAFFEINE (C) IN INFANTS UNRESPONSIVE TO THEOPHYLLINE (T) IN APNEA OF PREMATURITY.

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In order to determine if C is an effective treatment of apnea unresponsive to T, 8 premature infants ($\bar{x}$ GA = 31.5 wks, $\bar{x}$ BW = 1820 grams) with severe apnea despite therapeutic T levels were studied. A diagnosis of apnea of prematurity was made after a thorough evaluation failed to establish a definitive etiology. Infants were then treated with T, maintaining a serum concentration of 8-12 mg/l. Thermistor pneumocardiograms were performed on infants with persistent clinical apnea. Treatment failures were defined as a minimum of 2 episodes of $\geq$ 20 seconds of apnea associated with bradycardia ($<$ 100). Infants with central or mixed apnea were changed to C, maintaining a serum concentration of 8-20 mg/l. Cardiorespirograms were then repeated.

RESULTS:

Blood Levels	mean number of episodes of apnea				
$\bar{x}$ T/C (mg/l)	10-15 sec	15-20 sec	20 sec	Bradys	Periodic Breathing
8.4/2.3	7.4	6.4	7.3	10.4	4.0%
1.5/11.7	2.1	0.4	0.4	2.9	2.0%
	$p<.07$	$p<.02$	$p<.10$	$p<.05$	$p<.10$

A significant clinical improvement was observed in 7/8 infants. These data suggest that C may be effective in the treatment of apnea unresponsive to T. Since C has a wider therapeutic index and less side effects than T, it may be a more effective agent in the treatment of apnea of prematurity.

362 CARDIORESPIRATORY EFFECTS OF NALOXONE IN NEWBORN INFANTS.

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Naloxone (N) reduces the decrease in ventilation induced by hypoxia in healthy term infants. In addition, N by blocking endogenous opiates has a potential role in the therapy of hypotensive patients with septic shock and may allow the release of catecholamines. However, serial measurements of the cardiopulmonary effects of N in normotensive infants are not available. During active sleep we studied 8 term infants (mean age 1.9 days) and 8 preterm infants (mean gestational age 34 wks, age 2.1 days) who had recovered from transient respiratory distress, prior to removal of their umbilical arterial line. Heart rate (HR), aortic blood pressure (BP), transcutaneous PO_2 ($PtcO_2$), transcutaneous PCO_2 and respiratory frequency (RR) were measured before and 5, 10,15,20,25 and 30 minutes after administration of N (0.1 mg/kg IV) or placebo. A Dinamap BP monitor was used in 3 preterm infants. Plasma levels of epinephrine (E) and norepinephrine (NE) were also determined before and 10 and 20 minutes after N administration. Interestingly, 5 preterm infants increased their $PtcO_2$ and RR after N. However, there was no significant change in any cardiac or respiratory parameter measured in both groups of infants and levels of E and NE did not appreciably change following administration of N. There were no changes following placebo. Our findings indicate that in normotensive infants: 1)N does not have a major influence on BP, HR, oxygenation and ventilation; 2)levels of E and NE remain within normal range following administration of N.

363 EFFECT OF VASOACTIVE INTESTINAL PEPTIDE(VIP) ON REGIONAL CARDIAC FLOW IN THE AWAKE PIGLET.

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VIP is found in the heart and increases coronary blood flow (BF) in anesthetized dogs. BF was measured (radioactive microspheres) in 6 - 8 week old piglets during vehicle infusion and at 10 min of VIP (1µg/kg/min, iv; plasma VIP of 9±2ng/ml). VIP increased heart rate (228±14 vs 136±8* beats/min), reduced systemic pressure (64±5 vs 92±3*mmHg), reduced LA pressure (2±1 vs 7±2*mmHg), while CO was unchanged (276±30 vs 261±20ml/min/kg). There was no increase in LV, RV or atrial BF after 10 min of VIP infusion. In addition, regional vascular resistance was unchanged (table). VIP reduced stroke volume (1.3±0.2 vs 2.0±0.2* ml/min/kg/beat), stroke work (83±18 vs 182±22* units) and the LV endo/epi BF ratio (1.03±0.04 vs 1.23±0.06*). (*p<0.05)

	Flow(ml/min/g)		Resistance[$\bar{m}$Ao/(ml/min/g)]	
Region	Control	VIP	Control	VIP
LV Endo	3.01±0.21	2.27±0.32	31.8±3.1	33.8±7.3
Mid	2.94±0.27	2.34±0.37	32.3±3.1	33.6±7.3
Epi	2.46±0.18	2.24±0.34	38.7±3.2	34.8±7.3
RV Endo	2.30±0.12	2.51±0.41	40.8±2.8	31.8±6.9
Epi	1.7910.09	2.05±0.36	52.2±3.7	41.3±10.8
R Atrium	1.37±0.21	2.01±0.51	77.0±11.3	57.9±18.2
L Atrium	1.28±0.19	1.55±0.41	83.9±13.4	83.9±31.9

(Values are mean±SE; n=8)

Thus, VIP in awake piglets reduces stroke work, stroke volume, does not increase and causes a maldistribution in LV BF.

364 MATERNAL AND FETAL CARDIOVASCULAR RESPONSES TO SINGLE DOSE DIGOXIN ADMINISTRATION IN PREGNANT EWES.

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With increased number of pregnant cardiac patients, usage of Digoxin may be expected to increase. Also Digoxin has been used during pregnancy for the treatment of fetal arrhythmias. In order to explore the effect of Digoxin on uterine flow and on the fetus, fifteen experiments were conducted in seven chronically instrumented pregnant ewes. The animals were equipped with electro-magnetic flow meters in the uterine arteries and catheters inserted in the maternal aorta, fetal aorta and inferior vena cava. After obtaining baseline values, 1.2 mg Digoxin IV bolus injection, maternal observations were done at 15, 30, 45, 60, 90, 120, 150, 180 minutes. The fetal parameters were assessed at 30, 90, and 150 minutes after drug injection. Although 9 out of 15 experiments showed decreased uterine blood flow, the overall decrease was not statistically significant. In all 15 experiments the maternal heart rate and PCO_2 were noted to decrease ($p < .001$). The fetal blood pressure was found to decrease ($p < .001$), the PO_2 also decreased ($p < .05$), and the PCO_2 increased ($p < .001$). The maternal cardiovascular changes and possibly the Digoxin effect on the fetus can account for the above observations.

365 DEVELOPMENT OF PHENOBARBITAL GLUCOSIDATION IN THE HUMAN NEONATE.

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Phenobarbital-N-glucoside (PNG) has recently been identified as a significant metabolite of phenobarbital (PB) in man. Glucosidation is an uncommon metabolic pathway for drugs in mammals. Bilirubin is glucosidated as well as glucuronidated. However, few xenobiotics have been recognized to be metabolized through this pathway.

Four neonates treated with PB alone for seizures were studied. Serum concentrations ranged from 30 to 80 mg/l. Serial single daily voided urine specimens were analyzed for PB, PNG, and total p-hydroxyphenobarbital (PHPB). PHPB was first excreted on the 4th day of life in 2 patients and 10th day in 2. No PNG was detected by the 12th day in 1 case or 16th day in 2 cases. In the fourth case, the oldest by estimated gestational age, PHPB was first detected on day 4, and PNG on day 14. On day 20, PNG accounted for 50% of the drug excreted in the urine. Production of PHPB glucuronide was not assessed.

It appears that N-glucosidation is a significant route for PB metabolism in the neonate. This pathway develops rapidly but after aryl hydroxylation.

366 HEMODYNAMIC EFFECTS OF DOPAMINE.

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Dopamine (Dp) is widely used in the hemodynamic support of infants. Previous studies have shown contradictory effects of Dp on systemic and pulmonary vasculature. We hypothesized that oxygen status could affect the hemodynamic response to Dp. Seven healthy,<10 day old acutely instrumented lambs were studied. Catheters were placed in the pulmonary artery (Ppa), left atrial, inferior vena cava and descending aorta (Pas); and electromagnetic flow probe was placed around the main pulmonary artery ($\dot{Q}$pa). Doses of Dp (5, 10, 15 and 50 µ/Kg/min.) and PaO_2 status were randomized. Each dose of Dp was given for 5 min.

	NORMOXIA				HYPOXIA			
	5	10	15	50	5	10	15	50
$\bar{P}$as	-	-	-	↑	-	-	-	-
$\bar{P}$pa	-	↑	-	↑	-	↑	-	↑
$\dot{Q}$pa	-	-	-	↑	-	↑	-	↑
HR	-	-	-	-	-	-	-	↑

n=7; ↑=p<.05 by 2-way ANOVA.

The difference in response to each dose may be due to activation of different catecholamine receptors. If neonates with normal hearts respond in similar fashion to these lambs, Dp may not be an appropriate pressor in normoxia except at very high doses. We observed arrythmias in 1/7 animals at 50 µ/Kg/min. Also, Dp should be used with caution in hypoxic neonates because of the tendency for $\bar{P}$pa to increase while $\bar{P}$as remains unchanged. This could precipitate or worsen right-to-left ductus art. shunting.