356 PHARMACOKINETICS OF INTRAVENOUS VITAMIN E IN PRETERM INFANTS. Soraya Abbasi, Bradford K. Jensen, Lois Johnson, Mary Grous, Vinod K. Bhutani. Univ of PA Sch of Med, Pennsylvania Hosp., Newborn Pediatrics Phila PA and Hoffmann-LaRoche, Inc. Nutley, NJ.

Pharmacokinetics of vitamin E (E,mg/dl) were evaluated in 28 preterm infants following intravenous infusion of doses of dl- tocopherol (Hoffmann-LaRoche) administered over a period of 8 hours. Blood samples were obtained from a central line immediately prior to, and at 2,4,6,8,10,12,18,24,48 and 72 hours after E infusion. Dosages were: Group I, (n=4), (BW=1218 ±216, GA=29.5 ±2.6) = 5 mg/kg; Group II, (n=6),(BW=1091 ±165, GA=28.5 ±1.2) = 10 mg/kg; Group III, (n=7), (BW=1078 ±267, GA=27.5 ±1.2) = 15 mg/kg; Group IV, (n=6), (BW= 941 ±115, GA=27.5 ±1.2) = 20 mg/kg; Group V, (n=5), (BW=1040 ±193, GA=30.8 ±3.7) = 30 mg/kg. Pharmokinetic parameters were obtained by independent analysis of E concentration-time profile. Mean ±SD values for serum harmonic E half life (T1/2, hrs), volume of distribution (VD, L/kg), and serum clearance (sc, ml/kg/hr) for the groups are:

Gr	E,time	E,peak	E,24hrs	E,36hrs	T1/2	VD	SC
I	0.6 ±.3	2.6 ±1.1	1.7 ±.6	1.91	173.0	.42 ±.25	1.4 ± .2
II	0.6 ±.3	4.3 ±1.3	3.1 ±1.5	3.4 ±1.3	69.3	.31 ±.09	2.8 ± .9
III	0.7 ±.3	4.9 ±2.7	2.7 ±1.3	2.5 ±.8	53.4	.54 ±.26	4.5 ± .8
IV	0.7 ±.2	6.2 ±3.5	3.5 ±.9	3.6 ±.4	43.3	.50 ±.38	5.7 ±2.7
V	0.4 ±.3	5.7 ±1.6	3.3 ±1.2	-	138.6	.72 ±.20	3.0 ±1.4

Infants in Group I and V had additional supplemental E (multi-vitamin in hyperalimentation) resulting in fluctuation of base-line values and alteration of apparent half life. These data should be useful for determination of dosage recommendations.

●357 METABOLISM OF DOXAPRAM IN PREMATURE NEWBORNS. J.V. Aranda, A. Mandelberg, K. Beharry, J. Rex, O. Peleg, F. Eyal. Depts Pediatrics and Pharmacol, McGill Univ-Montreal Child. Hosp. Res. Inst., Montreal, Canada and Hadassah Univ-Mt. Scopus Jerusalem,Israel.

Doxapram (Dox), a respiratory stimulant in neonatal apnea, has a short pharmacologic effect (<1 hr) despite a reported prolonged plasma t 1/2 (7 hrs). Possible biotransformation to a metabolite (met) previously indistinguishable from Dox by GLC was studied in 6 prematures of bt wgts (1.41±0.14), gest. age (31.5±1.02), postnatal age (8.5±3.0) , given incremental Dox infusion of 0,0.1,0.5,1.0,2.5,5.0 mg/kg/h every 20 minutes. Blood samples were obtained at the end of each dose and plasma was assayed for Dox and mets (keto Dox or AHR 5955, AHR 0914, AHR 5904) by sensitive HPLC. Data show rapid biotransformation of Dox to Keto Dox (major met) which correlated to dose rate (p<0.01).

Time (min)	Dose infused (mg/kg/h)	Doxapram (mg/l)	Keto Dox AHR 5955 (mg/l)
0	0	0	0
20	0.1	0.80 (0.60-0.94)	1.23 (0.7-1.36)
40	0.5	0.92 (0.60-1.33)	1.43 (1.06-1.80)
60	1.0	1.25 (0.80-2.61)	2.3 (1.07-3.23)
80	2.5	0.98 (0.74-1.1)	2.7 (1.8-3.75)
100	5.0	1.08 (0.84-1.44)	4.9 (3.5-9.5)

Values are expressed as mean (range).

We conclude that the short effect of Dox is due to rapid metabolism. Pharmacodynamic activity of Keto Dox, and kinetics of disposition of Dox and metabolites require further investigation.

358 EFFECT OF THEOPHYLLINE ON PRETERM (≤32 WKS) PULMONARY MECHANICS. Vinod K. Bhutani, Thomas H. Shaffer, Soraya Abbasi and Emidio M. Sivieri. Spon. by: Lois H. Johnson. Univ of PA Sch of Med, Penna Hosp, Neo Pulm Lab, & Temple Univ Sch of Med, Dept of Physiol, Phila

Theophylline (theo) has been used in preterm neonates for apnea of prematurity (A&B) and to facilitate extubation. In addition to being a respiratory stimulant, theo is an airway smooth muscle relaxant. The role of theo on pulmonary mechanics of preterm neonates with compliant airways was evaluated to define the effect of airway smooth muscle relaxation. Fifteen preterm neonates (≤32 weeks gestation, ≤10 days postnatal age) who were administered theo for A&B or extubation were enrolled in the study. Pulmonary mechanics were determined prior to commencement of theo and 2-5 days subsequently. Mean theo level was 8.4 mg/dl). Signals of airflow and transpulmonary pressure, obtained during spontaneous breathing, were analyzed and recorded by the P8DS computer. Mean values for dynamic pulmonary compliance (C, ml/cm$H_2$0/kg); pulmonary resistance, resistive work of breathing: inspiratory, expiratory and whole breath (Ri, Re, R; cm$H_2$0/L/sec; and WOBi, WOBe, WOB; gm.cm/kg) before and on theo are listed:

	C	Ri	Re	R	WOBi	WOBe	WOB
Before	0.77	60	160	97	6.6	13.1	21.7
On Theo	1.12*	32*	117	64	4.3	7.6	12.0

Significant increases in C (* p<0.05) and decreases in Ri (* p<0.05) were demonstrated. Changes in Re were inconclusive because of high variability and may be explained by the propensity towards airway collapse. These data describe the changes in pulmonary mechanics due to the direct effects of theo on airway smooth muscle. (Supp. in part by NIH HL32031).

359 BLOOD PRESSURE CHANGES AFTER BOLUS INFUSION OF DOXAPRAM IN NEWBORN LAMBS. Pierre W. Blanchard, Steven Hobbs, Jacob V. Aranda, Michel A. Bureau. McGill University-Montreal Children's Hospital Research Institute, Dept. of Pediatrics, Montreal, Canada.

Doxapram (Dox) has been recently used in the treatment of apnea of the newborn. Currently Dox is given by continuous I.V. low dose infusion; this usually implies a slow onset of action. A bolus infusion as a loading dose should accelerate this onset of action, and in theory repeated boluses could be used for administration. However, increases in blood pressure (BP) have been identified when a continuous I.V. infusion is used. The objective of this study was to define the changes in BP following bolus doses of Dox: 1,2.5, 5 and 10mg/kg given over 1 min. Seven lambs were studied at 2 and at 15 days of age. After 1 mg/kg, 2 of the 7 two-day old lambs had no change in BP, the 5 others had a transient (<1 min) increase of a maximum of 10 mmHg from baseline; at 15 days of age, 2 had no change in BP, 2 had an increase of 5 to 10 mmHg (<1 min) and 3 had an increase of 10 to 20 mmHg (<2 min). After 2.5 mg/kg a maximum increase of 15 mmHg (<30 sec) was seen in 2 of the 2 day old lambs and in the 15 day old lambs a maximum increase of 30 mmHg (<1 min) was seen in 1 of the 7 lambs. For doses of 5 and 10 mg/kg the same magnitude of increase was seen but for a longer duration (5 to 30 minutes). In summary, only a transient mild increase in BP was seen with a rapid (1 min) bolus dose of 2.5 mg/kg or less of Dox. The safety of even these apparently small increases in BP is not yet known. Further, the effect of a less rapid infusion rate needs to be determined.

●360 VENTILATORY ($\dot{V}E$) RESPONSE TO INTRAVENOUS BOLUS OF DOXAPRAM (DOX) IN NEWBORN LAMBS. Pierre W. Blanchard, Steven Hobbs, Jacob V. Aranda, Michel A. Bureau. McGill University-Montreal Children's Hospital Research Institute, Montreal, Canada.

The $\dot{V}E$ response to I.V. bolus infusion of Dox is largely unkown, although Dox is used parenterally in the treatment of apnea of infancy. The objectives of this study were 1) to determine if $\dot{V}E$ response to Dox changes with post-natal age 2) to characterize the $\dot{V}E$ response to graded bolus doses of Dox (1 to 10 mg/kg) 3) to partition the peripheral versus the central chemoreceptor response to Dox. Seven intact lambs were studied at 2 and at 15 days of age. Two lambs had carotid body denervation (CBD) at 2 days and were studied at 7 days of age. The animals were studied awake and unsedated. $\dot{V}E$ was recorded before and continuously for 30 min. after 1 mg/kg Dox I.V. bolus. The study was repeated using 2.5, 5 and 10 mg/kg. The $\dot{V}E$ response was characterized by a diphasic pattern, an early peak and a late plateau. In the 2 day old $\dot{V}E$ increases rapidly from 550 to 900 ml/kg/min with 1 mg/ kg, returning to near baseline plateau in 10-12 min. With 2.5 mg/kg, the peak $\dot{V}E$ was 1000 ml/kg/min. With 5 and 10 mg/kg, the peak $\dot{V}E$ did not increase further but the plateau $\dot{V}E$ was shifted to higher $\dot{V}E$ levels. The same dose response and pattern was seen in the 15 day old lambs. The CBD lambs showed a similar pattern, but the peak response was decreased by more than 50%. Conclusions: 1) no postnatal maturational change was seen in the $\dot{V}E$ response to Dox 2) Doses >2.5 mg/kg did not increase the peak $\dot{V}E$ 3) the diminution of the $\dot{V}E$ by CBD suggests that the peak response is mediated by the peripheral chemoreceptors.

361 INDUCTION OF ARYL HYDROCARBON HYDROXYLASE (AHH) FORMS OF CYTOCHROME P-450 CAN BE MONITORED BY CAFFEINE URINARY METABOLITE RATIOS. M. E. Campbell, M. Long, W. Kalow, S. P. Spielberg, Depts. of Paediatrics and Pharmacology, University of Toronto, Div. of Clinical Pharmacology, Hospital for Sick Children, Toronto, Ontario.

A major biological effect of toxic environmental chemicals such as the dioxins and polyhalogenated biphenyls is induction of specific forms of cytochrome P-450 (AHH). There is a need for non-invasive approaches to monitoring effects of chemical exposures suitable for large population studies. Caffeine is metabolized in part by AHH. We have studied urinary metabolite products of caffeine as a means of determining AHH activity following ingestion of small doses of caffeine in beverages. In a study of 15 adult subjects, a good correlation was found between systemic caffeine clearance and urinary molar ratios of paraxanthine-7-demethylation products relative to a paraxanthine-8-hydroxylation product (r=0.91, p<0.001). In a larger population study, we found: 1. no gender differences in adults or prepubertal children; 2. no differences between Orientals (n=26) and Caucasians (n=42); 3. prepubertal children (n=21) showed a higher (p<0.001) mean metabolite ratio than adults (n=61); 4. oral contraceptive users (n=9) had lower (p<0.05) ratio than women not using oral contraceptives (n=30); 5. smokers (n=26) had a higher (p<0.001) ratio than non-smokers (n=61). In a separate study, an good correlation was found between the urinary metabolite ratio and caffeine clearance as estimated by the ^{13}C-caffeine breath test. Use of caffeine metabolite ratios in urine following ingestion of the compound in coffee or cola beverages provides a safe, inexpensive way of monitoring populations for induction of AHH, and for examining the effects of exposure to environmental chemicals early in life on the ontogeny and regulation of this important class of oxidative drug metabolizing enzymes.