367 EFFECTS OF A LEUKOTRIENE ANTAGONIST, FPL57231, ON THROMBOXANE B2 (TxB2) AND 6-KETO PGF1∝ LEVELS IN HYPOXIC PULMONARY HYPERTENSION (HPH) IN PIGLETS.

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The effects of FPL57231 on plasma levels of 6-keto PGF1∝ (6-keto) and TxB2, metabolites of PGI2 and thromboxane A2, were examined during ventilation with 12% O2 in 5 piglets (X±SD;wt, 3194±1311g;age,15±5d) treated with FPL57231 (2mg/kg x 10 min), and in 5 control piglets (C) (wt,2958±1103g;age,14±5d). Cardiac index, pulmonary artery (Ppa), systemic arterial, pulmonary wedge and right atrial pressures were measured; systemic and pulmonary vascular resistances (PVR) calculated. Levels of 6-keto and TxB2 were measured during normoxia (Norm BL), and after 20 (Hypoxic BL), 30,35 and 55 min (') of hypoxia. FPL57231 was infused after hypoxic baseline measurements were made until 30'.

X±SD; *ANOVA		Norm BL	Hypoxic BL	30'	35'	55'	P
TxB2	C	598±298	450±198	458±162	399±190	472±357	<.01*
(Pg/ml)	T	559±142	509±131	875±149	947±246	1013±226	
6-keto PGF1∝	C	440±118	371±145	386±138	381±150	391±150	=.05*
(Pg/ml)	T	493± 97	439±148	603±118	611±194	689±225	

Ppa and PVR were lower ($p<.05$) in treatment animals during the study period. There was no significant difference between normoxic BL and 55' TxB2 or 6-keto levels in (C) animals. FPL-57231 was associated with an increase in TxB2 and 6-keto, suggesting that at this dose, FPL57231 may have lipoxygenase blocking activity. The decrease in PVR and Ppa in the presence of increased cyclooxygenase products further supports the role of leukotrienes as possible mediators of HPH in piglets.

368 EVALUATION OF POTENTIAL NEPHROTOXICITY OF AMIKACIN AND TOBRAMYCIN IN PREMATURE INFANTS.

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The nephrotoxicity(NT)of aminoglycosides in premature infants is a still disputed problem. To assess and compare this possible side-effect of two widely used compounds, tobramycin (TB) and amikacin (AK) we determined serum creatinine (SCr), urine content of N-acetyl-beta-glucosaminidase (NAC) and blood drug levels in 28 prematures with proven or suspected infections. Fourteen infants(mean gest.age:32.1±2.1wK;mean weight:1.650)were treated with TB,4 mg/Kg/day,and 14(mean gest.age:31.7±1.8wK; mean weight: 1.690±351 g)with AK, 15 mg/Kg/day,both divided in two doses i.m. Blood and urine samples were collected on days 1 and 8 of therapy and 5 days after its suspension. NT was defined as a rise in SCr of 0.3 mg% and/or a significant increase in urine NAC excretion on day 8 of therapy (early NT) or on day 5 after suspension (late NT). Mean trough and 1 hr postdose serum levels of TB on day 8 of therapy were 1.60±0.8 and 6.6±2 ug/ml, respectively. For AK they were 8.2±3.1 and 27.1±5.2 ug/ml. Neither drug was detected in infant sera 5 days after cessation. Both groups had similar baseline SCr and urine NAC content. No infant developed early or late NT. These data indicate that at our doses TB or AK do not result in increased levels of SCr or enzymuria in premature newborns. In addition, our results do not show any significant difference in the 2 groups and therefore, the choice between TB and AK should depend on other consideration, such as susceptibility of the pathogen or therapy cost.

● 369 COMPARISON OF TOLAZOLINE INHIBITION OF NOREPINEPHRINE (NE) CONSTRICTION OF NEONATAL HIRCINE PULMONARY AND FEMORAL ARTERIAL RINGS.

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The effect of tolazoline (1×10^{-5}M) upon the NE concentration-response (C-R) relationship was compared in small (2-3 mm) pulmonary and femoral arterial rings from neonatal goats in the presence of beta-adrenergic blockade and inhibition of the neuronal and extra-neuronal uptake mechanisms. NE C-R curves performed with and without tolazoline in each type of artery allowed determination of pK_B for tolazoline by the dose-ratio method and of the shift of the NE C-R curve by tolazoline (ΔpED_{50} tolazoline). Results are as follows (mean ± SEM; n = 5; $p = -\log_{10}$).

	Pulmonary	Femoral
pED_{50} without tolazoline	7.23 ± 0.22	6.49 ± 0.42*
pED_{50} with 10^{-5}M tolazoline	6.38 ± 0.28+	5.62 ± 0.67*+
pK_B tolazoline	5.77 ± 0.23	5.79 ± 0.33
ΔpED_{50} tolazoline	0.85 ± 0.20	0.86 ± 0.29

(*Significantly different from corresponding pulmonary value; +Significantly different from corresponding value of same vessel without tolazoline; 2-way ANOVA). The pulmonary NE C-R curve is to the left of that of the femoral; however, the effect of tolazoline on the NE C-R curve is not different in the two vessels (pK_B tolazoline and ΔpED_{50} tolazoline not different; paired t-tests). These results do not support a difference in the sensitivity of pulmonary and systemic vessels to the α-adrenergic blockade of tolazoline in neonates.

† 370 NOREPINEPHRINE (NE) CONCENTRATION-RESPONSE (C-R) RELATIONSHIPS IN KREBS-PERFUSED NEONATAL LAMB LUNG AND HIND LIMB.

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C-R curves to NE (1×10^{-8}M to 1×10^{-2}M) were performed in Krebs-perfused neonatal lamb lungs and hind limbs in the presence of beta-blockade and inhibition of the neuronal and extra-neuronal uptake mechanisms. Response at each NE concentration is expressed as percent of maximum response for a given vascular bed in an animal. Results of C-R curves (mean [SEM]; n = 5) are as follows:

NE (M)	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
Pulmonary	6.4(1.7)	19 (2.9)	47(1.6)	78(6.3)	91(4.5)	98(2.1)
Hind Limb	1.3(0.5)	4.6(1.6)	28(6.0)	53(9.9)	85(10.3)	92(5.7)

(Curves significantly different; 2-way ANOVA) Results of changes in vascular resistance (ml/[kg·mm]; mean [SEM]; n = 5):

	Baseline	Maximum	Maximum Δ	Maximum % Δ
Pulmonary	6.1(20)	10(3.8)	4.4(1.9)	70(17)
Hind Limb	16(4.6)	62(12)	47 (13)	510(141)

(All pulmonary vs. femoral values significantly different, paired t-tests.) When response is expressed as % maximum for an individual vascular bed, the pulmonary C-R curve is to the left of that of the hind limb. However, pressure (not shown), resistance and changes in resistance are always much greater in the hind limb. These results do not support a role for increased sensitivity of the pulmonary bed to circulating NE in the pathogenesis of persistent transient circulation.

371 EFFECT OF NOREPINEPHRINE (NE) ON VASCULAR PROSTACYCLIN (PGI_2) SYNTHESIS IN THE KREBS-PERFUSED NEONATAL LAMB LUNG AND HIND LEG.

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PGI_2 synthesis by Krebs-perfused neonatal lamb lungs and hind limbs was quantified by RIA determination of 6-keto-$PGF_{1\alpha}$ (6K). Perfusates were collected during a 10-min control period, a 5-min perfusion with 10^{-6}M NE and three successive 10-min post-NE control periods. Results of 6K synthesis, ng/min; mean (SEM); n = 6:

Period	Control	NE	Post I	Post II	Post III
Lung	2.8(1.1)	2.6(0.6)	3.3(1.0)	3.3(0.9)	3.3(1.1)
Hind Limb	0.8(0.2)	1.1(0.3)	1.4(0.6)	1.2(0.6)	1.1(0.6)

There are no differences between the 5 time periods; pulmonary synthesis exceeds hind-limb synthesis throughout ($p < .001$, 2-way ANOVA). Results of perfusion pressures during these constant flow studies:

Period	Control	NE	Post I	Post II	Post III
Lung	7.2(1.1)	9.0(0.9)	7.8(1.0)	7.6(1.1)	7.4(1.1)
Hind Limb	12.5(1.9)	40.5(16)	16.2(2.0)	14.5(1.8)	14.1(1.9)

NE results in significant constriction in both vascular beds ($p < .05$); hind limb pressure exceeds pulmonary pressure ($p < .001$, 2-way ANOVA). Thus, unlike hypoxic pulmonary vasoconstriction, adrenergic vasoconstriction does not cause demonstrable augmentation of PGI_2 synthesis in either lung or hind limb.

† 372 SUSTAINED RELEASE THEOPHYLLINE (SRT): ABSORPTION IN YOUNG CHILDREN.

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Available reports concerning the use of SRT in preschool children are limited to evaluations of single daytime dosing intervals with no data regarding the rate or extent of theophylline absorption. This study was performed to examine SRT absorption over multiple dosing intervals in young children. Eight asthmatic children, ages 2-6 yrs, were selected. After an IV aminophylline study to obtain essential pharmacokinetic parameters, each child received Slo-Bid Gyrocaps (S-B, Rorer) q 12 hrs and Slo-Phyllin Gyrocaps (S-P, Rorer) q 8 hrs for 7 days each. On day 7 of each study period, serum theophylline concentrations (STC) were obtained every 2 hrs for 24 hrs and absorption over time calculated. By generally applied parameters, including mean STC, total bioavailability, and % change in STC over a single dosing interval, the preparations did not differ. However, a more detailed evaluation of absorption revealed a marked difference between the two preparations. S-B was essentially 100% bioavailable at both the morning (97 ± 9% SEM) and evening (99 ± 10%) doses and showed a consistent rise in STCs to a peak 4-6 hrs after each dose. S-P, on the other hand, showed no consistent peak-trough effect and had considerable dose-to-dose variation in % bioavailability (0800 hrs - 102 ± 14; 1600 hrs - 77 ± 15; and 2400 hrs - 141 ± 13). These differences indicate delayed and then overlapping absorption with the 1600 and 2400 hr doses, respectively. In summary, analysis of dose-to-dose absorption was required to reveal the difference between the two study preparations. Comparison of theophylline preparations by standard techniques appears inadequate for evaluation of therapeutic value.