▲374 THROMBOXANES: THE LINK BETWEEN INTRALIPIDS AND PULMONARY VASOCONSTRICTION IN THE NEWBORN.
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During intralipid (IL) infusion, premature neonates demonstrate significant decreases in pO which are accompanied by pulmonary vasoconstriction. The mechanism by which intralipids induce these changes is not yet known. This study was undertaken to evaluate the hypothesis that IL, via the provision of increased fatty acid precursors, acts by increasing biosynthesis of the vasoconstricting prostanoid, thromboxane.

Thirteen neonates (<1750 grams) who had not yet been fed, and were not expected to receive any enteral nutrition for 5 days were randomized to receive either TPN with IL (n=7) or TPN without IL (n=6). Plasma prostanoid levels were drawn on day 1, 3 and 5 of study and results are as follows:

	TxB_2		6 Keto PGF_1	
	TPN	TPN + IL	TPN	TPN + IL
DAY 1	302±257	417±200	203±189	171±147
DAY 3	187±109	427±188	187±103	248±158
DAY 5	148±92	924±498	224±116	215±118

The data are consistent with the following conclusions: 1. IL provide increased essential fatty acid prostaglandin precursors; 2. These increased EFA precursors result in increased biosynthesis of the vasoconstricting prostanoid, thromboxane; and 3. Thromboxane thus produced may contribute to the observed pulmonary vasoconstriction.

375 DEVELOPMENTAL PATTERN OF AMINOGLYCOSIDE DISPOSITION IN PREMATURE INFANTS: BI-PHASIC CHANGES IN SERUM CLEARANCE.
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Previous studies evaluating aminoglycoside (A) disposition in premature infants have described the relationship between various indices of maturation and serum A clearance as either linear or exponential. Pharmacokinetic studies carried out in 992 infants demonstrated a distinctly bi-phasic pattern when indices of A elimination are compared to indices of maturation. Gestational age (GA) 24-39 wks, postnatal age (PNA) 1-20 wks, postconceptional age (PCA) 25-53 wks, birthweight (BW) 380-3950 gm and study weight (SW) 350-4620 gm were recorded. Serial A serum concentrations were determined by RIA. Volume of distribution (Vd) 0.29-0.63 L/kg, elimination rate constant (Ke) 0.029-0.231 hr-1, and serum clearance (Cl) 0.0056-0.630 L/hr were calculated. When Ke and Cl were compared to GA, PCA, BW and SW, the relationship was distinctly bi-phasic. Prior to 34 wks GA and 35 wks PCA, Ke and Cl increased slowly with respect to increased GA and PCA. After 35 wks GA and 36 wks PCA, Ke and Cl increased rapidly with respect to increasing GA and PCA. These changes at 34-36 wks may represent a functional change in the neonatal kidney at this stage of maturation. Vd (L/KG) was found to decrease slightly with increasing GA, PCA, BW and SW. This data suggests that neither a linear nor exponential model fully describes the improvement of A Cl in the neonate. A biphasic model with a breakpoint at 34 wks GA or 35 wks PCA appears to be the most appropriate description of the improvement. Therefore, GA and PCA are important variables to evaluate in the determination of A dosing recommendations.

●376 SYSTEMIC PRODUCTION OF VASODILATOR EICOSANOIDS IS NOT INCREASED IN INFANTS WITH SYMPTOMATIC PATENT DUCTUS ARTERIOSUS (SPDA) WHO FAIL INDOMETHACIN PROPHYLAXIS.
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To determine whether altered production of vasoactive eicosanoids precedes the development of symptomatic patent ductus arteriosus (SPDA) in infants who have received prophylactic indomethacin (I), major urinary metabolites of thromboxane, prostacyclin and PGE_2 were measured by gas chromatography-mass spectrometry. The 4 infants (26-27 wks gestation; 840-870 gm birth weight), 2 of whom had SPDA on days 6 and 11 were matched for birth weight, gestational age, race, severity of hyaline membrane disease and intensity of ventilatory support. All received prophylactic I, 0.2 mg/kg 24 hr after birth. Serum I was 582-1283 mg/ml and 155-960 ng/ml 24 and 96 hrs post dose respectively. There were no differences in urinary PG excretion patterns between infants who were protected and infants who developed SPDA, except that the symptomatic infants showed marked suppression of PG excretion when given additional I as treatment. Failure of I to protect against SPDA appears unrelated to systemic production of vasoactive PGs. Serum levels of I did not discriminate babies likely to develop SPDA despite prophylactic treatment. There appears to be no rationale for increasing the prophylactic dose of I to afford greater protection from SPDA. The role of PGs in the onset of SPDA following prophylactic I remains to be elucidated.

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377 THE PIGLET AS A MODEL FOR CEFONICID PHARMACOKINETICS.
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The piglet is a useful pharmacodynamic model for the study of catecholamines and an acceptable pharmacokinetic (PK) model for methylxanthines. We evaluated the piglet as a model for the PK of cefonicid, a second generation cephalosporin. Cefonicid (C) PK were evaluated in 13 piglets at 3 (n=6) and 6 (n=7) days of age. Following a single I.V. dose of 50 mg/kg, blood samples (n=10) were obtained over 24 hr. Serum ultrafiltrate was prepared for determination of unbound C by membrane centrifugation, and C was quantitated by HPLC (LLD = 5 mg/L; C.V. <10%). ESTRIP was used to generate polyexponential parameter estimates necessary for PK calculations. No significant differences were found between the 3 and 6 day old animals with respect to $T_{\frac{1}{2}}$ (1.4±0.1 vs. 1.04±0.07 hr), total clearance (CL; 0.39±0.03 vs. 0.31±0.07 L/hr/kg) or Vd(area) (0.3±0.04 vs. 0.28±0.06 L/kg). The PK parameters for C in the piglets were markedly different from those in young adult humans ($T_{\frac{1}{2}}$=4.8 hr; Vd=0.12 L/kg), as was true for the free fraction of C from piglets (93.0%) vs. healthy adults (3.1%). Comparison of piglet serum to that from human neonates revealed a significant difference in the albumin concentration (1.5±0.2 gm% for piglet vs. 4.3±0.2 gm% for human) and the total protein:albumin ratio (2.7±0.3 for piglet vs. 1.5±0.1 for human). The markedly increased CL of C in the piglet may be consequent to interspecies differences in C protein binding. Our data suggest that the piglet may not be an adequate model to evaluate the PK of C for extrapolation to the human infant.

●378 **PHARMACOKINETICS AND RESPIRATORY PHARMACODYNAMICS OF IV SALBUTAMOL IN NEONATES WITH BRONCHOPULMONARY DYSPLASIA**
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Attempts to wean ventilator-dependent infants with BPD have been made by trying to reduce bronchospasm using β agonist drugs or caffeine. However, all drugs tested to date were not β2 selective and their use has been associated with unaccepted tachycardia. We studied the pharmacokinetics and respiratory dynamics of salbutamol after an IV infusion of 1 µg/kg/mn over 30 min. Our patients were 6 ventilatory dependent infants with BPD (24-28 wks gest. age; 50-90 days postnatal age). Serum concentrations were measured by a new HPLC method. Elimination T1/2 of salbutamol was 133 ± 27 min (mean ± SEM). Calculated distribution volume was 129 ± 397 ml/kg and clearance rate of 7.5 ± 2.6 ml/kg/min. The shorter T1/2 in these patients when compared to healthy adults or patients with CF may be explained by smaller Vd in the presence of comparable clearance. Passive expiratory, total respiratory system compliance (CRS) improved in all infants (mean 23%) though in only 5/6 was this an immediate effect. Airflow resistance decreased in 5/6 patients, (mean 23.3%). No consistent changes lasting for more than 1 hour were seen with Tc O2, Tc CO2, arterial or capillary CO2 or O2. All 6 infants developed tachycardia (from158±2/min to202 ± 6/min), which peaked at the end of the infusion. There was a significant positive correlation between Vd and % change in heart rate. Traditionally, it was thought that during the postnatal period β agonists do not exert bronchodilatatory effects due to the lack of β2 receptors. The present study indicates that the emergence of these receptors starts to take place in the postnatal period.

379 **THE EFFECT OF PHYSICIANS' COMPLIANCE ON RELAPSE RATE IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN**
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Despite significant improvement in the induction of treatment for ALL relapse rates during maintenance therapy are still relatively high. Putative mechanisms for maintenance failure include patients' compliance, pharmacokinetic variability of 6 mercapto purine (6MP) and methotrexate (MTX), as well as differences in tumor sensitivity. However, the issue of physicians' compliance with the recommended doses of chemotherapy as a factor affecting outcome has not yet been addressed. We studied the prescription patterns of maintenance therapy for children with ALL and their association with duration of complete remission. Both 6MP and MTX were prescribed in doses significantly lower than those recommended during maintenance therapy. Out of 212 evaluated patients, relapsed patients (n = 101) received significantly less MTX as compared to nonrelapsed patients (n = 111) during the first 2 years of maintenance therapy (p<.05).

In the group of standard risk patients who received the same induction therapy (n = 92), 11/17 (64%) of those receiving less than 50% of their recommended MTX dose relapsed, significantly more than those receiving more than 50% of the dose (28/75;37%) (p<0.05).

It is concluded that physicians' failure to adhere to the recommended protocol is associated with a higher relapse rate of ALL. Improved physicians' compliance may improve the prognosis of this fatal disease.