373 SELECTIVE INHIBITION OF THROMBOXANE (Tx) SYNTHETASE PREFERENTIALLY REDUCES SEPTIC PULMONARY HYPERTENSION IN PIGLETS. Cathy Hammerman, William Meadow, Elene Strates and Hui-Hsin Wu. (Spon. by K.S. Lee) University of Chicago, Department of Pediatrics, Chicago, Illinois.

Non-specific inhibition of prostaglandin (PG) synthesis reduces elevated pulmonary artery pressure (PAP) in animal models of newborn sepsis. We hypothesized that Tx was the PG which mediated the septic pulmonary hypertension, and investigated the effects of selective inhibition of Tx synthetase during Group B Streptococcal (GBS) sepsis in piglets.

4 piglets were anesthetized, intubated, ventilated and instrumented. Plasma Tx and prostacyclin (PC) metabolites were determined by RIA. Pulmonary hypertension was induced by continuous infusion of GBS. After induction of sepsis, PAP rose from 13±2 (SEM) to 42±5 mmHg, and cardiac output (CO) dropped from 104±6 to 52±6. BP remained unchanged. Concurrently, TxB_2 levels rose from 451±264 to 3370±610 pg/ml ($p<0.05$) and 6 keto $PGF_{1\alpha}$ levels rose from 323±55 to 1322±569.

While GBS infusion continued, a thromboxane synthetase inhibitor, dazemgrel (Dz)(UK 38485) was then administered at 1 mg/kg. In response to treatment, PAP decreased rapidly to 16±1 mmHg, BP and CO remained stable. TxB_2 levels dropped to 1960±360 and 6 keto $PGF_{1\alpha}$ (a prostacyclin metabolite) levels increased to 2090±363.

Conclusions: 1.GBS elevated PAP in piglets while raising both TxB_2 and PC metabolites. 2.Dz selectively reduced TxB_2 and shunted PG production towards PC. 3.Dz preferentially diminished PAP during GBS sepsis. 4.Selective inhibition of specific prostaglandins may benefit septic infants with elevated PAP.

● 374 DILATOR PROSTAGLANDIN LEVELS AND INDOMETHACIN RESPONSIVENESS. Cathy Hammerman, William Zaia, Stuart Berger, Elene Strates and Abdul Aldousany. (Spon. by K.S. Lee) Univ. of Chicago, Dept. of Pediatrics, Chicago, IL

Ductal patency in the premature is associated with increased concentrations of dilator prostaglandins. Indomethacin is a general inhibitor of prostaglandin synthesis; therefore, it is more likely to be successful if levels of dilator prostaglandins are elevated than if not. Both 6 keto $PGF_{1\alpha}$, a stable metabolite of prostacyclin, and PGE_2 have been demonstrated to be increased in conjunction with patent ductus arteriosus. Plasma levels of these prostaglandins were measured by radioimmunoassay in ten prematures with PDA. Four of the ten infants studied had elevated 6 keto $PGF_{1\alpha}$ levels (>500 pg/ml). All of these had a complete disappearance of their PDA murmur at 48 hours post therapy. Six infants had 6 keto $PGF_{1\alpha}$ levels within normal limits. Of these, four had no response to indomethacin and were surgically ligated, and two had transient decreases in the intensity of their murmurs with subsequent recurrences. PGE_2, in general, varied in the same direction as did 6 keto $PGF_{1\alpha}$, however it was less sensitive in predicting therapeutic response. Thus, elevation of 6 keto $PGF_{1\alpha}$ is closely correlated with indomethacin responsiveness.

6 keto $PGF_{1\alpha}$	48 hour response	PGE_2
153	None	82
160	None	<50
<500	None	<100
<500	None	<30
<250	Murmur Softer	<50
<500	Murmur Softer	<100
662	Murmur Gone	59
1177	Murmur Gone	<100
1300	Murmur Gone	207
1095	Murmur Gone	208

● 375 EFFECTS OF ADOLESCENT DEVELOPMENT ON THEOPHYLLINE HALF-LIFE Karen Hein, Ralph Dell, Mike Pesce, Ella Copoulos, Marion Miller Albert Einstein College of Medicine; Columbia University, Bronx Mun. Hosp. Ctr. and Babies Hosp., Depts. of Peds., N.Y.

Theophylline half-life ($t_{\frac{1}{2}}$ elim) is shorter in children than adults. To test the hypothesis that the increase occurs during adolescence, we studied 39 asthmatics aged 8-18y (mean 12.7). Twenty-five patients were male, 14 female. Tanner Stages I:13 patients, II:9, III:4, IV:4, V:9. After at least 2 weeks of long-acting theophylline, patients took 4 doses (24 hr.) of short-acting theophylline, prior to the study day. Following a single dose of short-acting theophylline (4-6 mg/kg) PO or IV, timed serum samples (minimum 3, maximum 22 samples per patient) were obtained between 6-24 hrs. after dose. Duplicate samples were analyzed by fluorescent polarization technique (coef. of variation 5% at 2-40 μg/ml). $T_{\frac{1}{2}}$ elim calculated from serum levels ranged from 2.8 – 8.5 hr.

Tanner Stage	# of Patients	$t_{\frac{1}{2}}$ (hr.) Mean	± S.D.
I	13	5.40	1.54
II-IV	17	5.66	1.54
V	9	7.22	1.45

$T_{\frac{1}{2}}$ correlated with age $p<.01$ ($r^2=0.2$) and Tanner Stage $p<.01$ ($r^2=0.2$). Mean $t_{\frac{1}{2}}$ of females (6.54 hr.) was longer than males (5.59). Puberty, (defined by age or Tanner Stage) accounts for 20% of the variability, whereas genetically determined rates of metabolism and environment probably account for much of the remaining inter-individual variation in $t_{\frac{1}{2}}$. During puberty, changes in body composition and liver function occur which may influence drug distribution and metabolism, thereby contributing to the increase in drug $t_{\frac{1}{2}}$. Regardless of the mechanism, since $t_{\frac{1}{2}}$ increases during adolescence, theophylline dose and interval need to be adjusted carefully during the teenage years.

376 AGE-DEPENDENT VERAPAMIL KINETICS AFFECT PEDIATRIC ORAL DOSE REQUIREMENTS* P. Hesslein MD, R. Gow MD, J. D'Souza PhD, C. Finlay BSc, S. MacLeod MD, R. Rowe MD The Hospital for Sick Children, Toronto, CANADA

Although intravenous verapamil effectively terminates supraventricular tachycardia (SVT) in children, its utility as a chronic oral antidysrhythmic drug has been disappointing. To assess whether drug kinetics contribute to this problem, we measured serum concentrations before and for 24 hours after a maintenance oral dose of verapamil (mean dose 1.36 mg/kg, range 0.4-2.9 mg/kg) in 7 children with a median age of 10.8 yrs (range 2.8-15.3 yrs). All had SVT controlled by chronic oral verapamil at mean serum peak and trough concentrations of 248±117 and 64±38 ng/ml, respectively.

We found several clearly age-dependent kinetic parameters: younger children demonstrated faster drug uptake "Tmax" ($p<.005$), lower relative bioavailability "F" ($p<.01$), smaller volume of distribution "Vd" ($p<.005$) and slower elimination half-life "$t_{\frac{1}{2}}\beta$" ($p<.001$). Younger children also exhibited a possible diurnal variation in drug kinetics. There was no significant age-relationship in distribution half-life "$t_{\frac{1}{2}}\alpha$" or drug clearance rate.

Although these changes have opposing effects on serum concentrations, their net effect in young children is for a greater dosage requirement, and perhaps a shorter dosage interval, than are currently recommended.

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= 377 EFFECT OF VASOACTIVE INTESTINAL PEPTIDE(VIP) ON CEREBRAL BLOOD FLOW IN THE AWAKE PIGLET, Elizabeth L. Hohmann, Elizabeth Lorenz, Joseph A. Rysavy, Gunnar Lund, Stanley Einzig. Univ. of Minnesota, Pediatrics, Mpls.

VIP relaxes cerebral vessels in vitro. Central nervous system (CNS) blood flow(BF) was measured (radioactive microspheres) in 6 - 8 week 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, $p<.001$), reduced systemic pressure (64±5 vs 92±3mmHg, $p<.001$), while CO was unchanged (276±30 vs 261±20ml/min/kg). Caudate nucleus, cerebral gray and white matter BF was reduced by 19 to 25% while regional resistance was unchanged. In contrast, resistance was reduced by 23-34% in the spinal cord, brain stem and cerebellum while BF was unchanged.

	Flow(ml/min/g)		Resistance[mAo/(ml/min/g)]	
Region	Control	VIP	Control	VIP
Spinal cord	0.32±0.02	0.32±0.04	294±20	220±25*
Medulla	0.55±0.04	0.58±0.04	174±16	113±11*
Pons	0.80±0.12	0.71±0.06	132±18	96±14*
Dorsal Thalamus	0.94±0.11	0.88±0.10	111±17	84±16*
Cerebellum	0.96±0.07	0.86±0.05	100±9	77±10*
Caudate Nucleus	1.07±0.08	0.87±0.08*	92±14	82±16
Cerebral Gray	1.26±0.07	0.95±0.08*	76±8	67±6
Cerebral White	0.53±0.05	0.41±0.03*	186±24	167±18

Values are mean±SE; n=8; *$p<0.02$ to <0.005 vs Control

Thus, VIP induced CNS BF changes in awake piglets are different than in anesthetized animals. Whether this represents differential regional sensitivity to VIP or is a consequence of the systemic effects of VIP is unknown.

378 PHARMACOKINETICS OF NETILMICIN IN THE VERY IMMATURE PRETERM INFANT. A. James, K. Karmer, R. Couch, N. Holford, (Sponsored by P.R. Swyer), Depts. Paeds. National Women's Hosp. & Clinical Pharmacology, University of Auckland, Auckland, New Zealand.

Netilmicin, an ethyl derivative of dehydrogenated gentamycin C1a, is the most recent addition to the aminoglycoside group of antimicrobial agents and is claimed to have less ototoxic and nephrotoxic potential than gentamycin. Twelve very immature preterm infants received therapy with ampicillin and netilmicin for suspected or proven sepsis. The median gestational age was 27 weeks (range 26-32 weeks), and the mean birth weight 1070 grams (range 760-1660 grams). They received 2.5 mg/kg 12 hourly by short intravenous infusion during the first week of life, and 2.5 mg/kg 8 hourly subsequently. Serum pharmacokinetics of netilmicin were determined after the initial dose of netilmicin. Serum trough levels were estimated 2-5 days after the commencement of therapy. The mean serum peak level 60 minutes after infusion was 5.9 mg/L, and the mean trough level was 1.8 mg/L. Elimination half lives correlated inversely with gestational and chronological age. In very immature preterm infants, the mean half lives were 8.4 hours in infants <7 days of age, and 3.6 hours in those age >7 days. The drug was well tolerated and no adverse effects were observed.