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ALTERATIONS IN RENAL FUNCTION AS A RESULT OF PROLONGED IN-UTERO RITODRINE (IUR) EXPOSURE. R.Porat, P. Nuchpuckdee, and N. Brodsky. (Spons. by Hope Punnett) Albert Einstein Med., Ctr., and Temple Univ., School of Med., Dept., of Ped., Phila., Pa.

Ritodrine (R), a B-sympathomimetic tocolytic agent, has been reported to cause metabolic and cardiovascular changes in both mother and fetus. Recently, reduced inulin clearance, increased plasma renin activity, and increased urinary arginine vasopressin excretion were demonstrated on day 1 in infants exposed to IUR. These renal function tests, however, are not clinically applicable. We compared serum creatinine (Cr) in 10 IUR-exposed infants (mean R exposure 6.7 ± 4.8 days) and 11 controls (C) in the first week of life. There was no significant difference between R and C groups in gestational age (30.6 ± 1.4 vs 29.6 ± 2 wks), weight (1308 ± 247 vs 1195 ± 359 grms), or apgar score at 1 (5.5 ± 1.4 vs 5.3 ± 3.3) and 5 minutes (7.5 ± 1.1 vs 8.0 ± 1.4).

	Day	0	1	2	3	4	5	6	7
C Cr		0.87 [†] ±.14	1.00 ±.11	1.01 ±.15	1.00 ±.21	0.97 ±.13	1.01 ±.01	0.90 ±.12	0.90 ±.12
R Cr		1.06 ±.22	1.25* ±.23	1.35* ±.34	1.27* ±.29	1.25* ±.29	1.18* ±.12	1.23* ±.13	1.09 ±.27

[†] mean $\pm$ SD *P < .05

Infants exposed to prolonged IUR demonstrated increased Cr on days 1 through 6. None demonstrated clinical signs of renal failure. Careful monitoring of renal function, fluid, electrolytes and therapeutic drug levels is indicated in infants with prolonged IUR.

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PARENTERAL ANTIBIOTICS AND LACTOSE INTOLERANCE: ANOTHER SOURCE OF MORBIDITY IN TERM INFANTS. Alton R. Prihoda, Jatinder Bhatia and C. Joan Richardson (Spon. by David K. Rassin), University of Texas Medical Branch, Department of Pediatrics, Galveston, Texas.

The role of parenteral ATX as a cause of diarrhea in neonates has not been established. The aim of the present study was to determine the incidence of ATX-associated diarrhea and to test the hypothesis that diarrhea was due to lactose intolerance (LI). Presence of fecal reducing substances (+RS), stool frequency (SF) and consistency and requirement for dietary manipulation (DM) were monitored for 5 days in a group of term neonates receiving parenteral ampicillin and gentamicin (EXPT) and a group of control infants. Infants were either fed a standard lactose-containing formula (80%) or were breast fed (20%). Data (Mean $\pm$ SD):

GRP	N	BW (g)	GA (wks)	ATX	Feeding	% +RS	% stool	% Inf.
EXPT	25	3324 $\pm$ 648	39.2 $\pm$ 1.0	6.5 $\pm$ 6.2	30.2 $\pm$ 17.7	30.0*	80*	
CONT.	25	3495 $\pm$ 465	39.2 $\pm$ 1.0	--	9.1 $\pm$ 5.3	2.5	20	

Twenty of 25 EXPT infants developed watery stools with +RS compared to 5 of 25 control infants. DM and SF were also significantly ($p < 0.001$) greater in EXPT than in control infants. Of the EXPT infants, 10/5, 15/8 and 36/8% demonstrated LI within 12, 24 and 36 hrs. of feeding, respectively, with 89% of infants manifesting the same by 60 hrs. We conclude that parenteral ATX are associated with LI in term neonates and suggest infants demonstrating LI be placed on non-lactose containing formulas for the duration of ATX therapy.

* $p < 0.001$ vs control

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FUROSEMIDE GLUCURONIDATION IN INFANTS: IMPLICATIONS OF BETA-GLUCURONIDASE RESISTANT ISOMER FORMATION. Avinoam Rachmel and Wayne R. Snodgrass (Spon. by Michael A. Linshaw). Departments of Pediatrics and Pharmacology-Toxicology, Univ. of Kansas Medical Center, Kansas City, KS.

Furosemide (F) glucuronidation has been inconclusively suggested to affect the age-related increase in F clearance in infants. A specific high pressure liquid chromatography (HPLC) method for direct determination of furosemide glucuronide (FG) was developed. This method revealed the presence of beta-glucuronidase resistant (BG-R) isomers of FG, a phenomenon previously described for ester glucuronides. At neutral to mild alkaline conditions (pH 6.8-8.6, 37°C, 3 hours) FG, purified from both human urine and incubation of F and uridine diphosphoglucuronic acid in rat liver microsomes, partially isomerized to BG-R forms. Sodium hydroxide (NaOH) hydrolysis recovered all the F from all FG forms. In 6 sick infants (EGA 28-35 wks; ages 7-80d) given 1 or 2 mg/kg F i.v., 12 hour urine collections for determination of total FG (NaOH sensitive), BG sensitive FG (bovine enzyme, pH 5.2, 37°C, 1 hr) and direct FG measurement (HPLC) showed: (1) FG accounted for 7-37% of urinary F excretion, (2) urine kept at pH < 5 had no significant difference in FG content by any of the assays, and (3) urine stored frozen at pH 7.0 contained 0-69% of FG as BG-R isomers. We conclude: (1) BG resistant isomers of FG may form under physiological conditions, and (2) formation of these isomers can occur in vitro as a methodologic artifact. We speculate that the possible in vivo formation of BG resistant isomers of FG has implications for F enterohepatic cycling and disposition.

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EFFECT OF HUMAN GROWTH HORMONE (hGH) ON ACETAMINOPHEN (APAP) ELIMINATION: Geoffrey P. Redmond, O.P. Schumacher, Sally Terrentine, Charles Pippenger (Spon. by Paul G. Dymant). Depts. of Endocrinology, Pediatrics and Biochemistry, The Cleveland Clinic Foundation, Cleveland, Ohio

Previous work has indicated that hGH has quantitatively significant effects on drug elimination in human children. For many substrates, such as amobarbital, which are metabolized by the hepatic MFO system, elimination is slowed (G.P. Redmond, et al. Clin Pharmacol Ther 24:213, 1978). We wished to determine whether hepatic conjugation reactions are also altered by hGH treatment. 5 children were given APAP orally in a dose of 10 to 15 mg/kg before and again 6 weeks after hGH replacement therapy. hGH was generously supplied by the National Hormone and Pituitary Program (NHPP); all children met NHPP criteria for hGH deficiency. Preliminary results on 3 children are as follows:

	BEFORE hGH	AFTER hGH
T _{1/2}	1.67 hours	1.80 hours
Vd	647 ml/kg	719 ml/kg
Cl	277 mg/kg-hr	284 ml/kg-hr

These results indicate that elimination of APAP by hGH deficient children is similar to the 1.74 hr T_{1/2} observed in normal febrile children (J.T. Wilson, et al. Ther Drug Monitoring 4:147, 1982). hGH replacement did not affect T_{1/2}, Td or Cl. Studies of urinary metabolites are in progress to determine whether the ratio of sulfate to glucuronide is altered.

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RATIONAL DOSING OF RANITIDINE(R) IN PEDIATRIC ULCER DISEASE(UD). Michael D. Reed, Fred C. Rothstein, Carolyn M. Myers, Cheryl A. O'Brien and Jeffrey L. Blumer, Case Western Reserve University School of Medicine, Rainbow Babies & Childrens Hospital, Department of Pediatrics, Cleveland, Ohio 44106

Dosing requirements for R were determined in 10 children (C) aged 3.5-16 yr with endoscopically proven UD. Gastric acid output (GA) was monitored continuously during the first 2 days of therapy. The therapeutic endpoint was suppression of GA by $\geq 90\%$. C received 0.06mg R/kg over 15 min plus an infusion of 0.02mg R/kg/hr. Each hour they received a bolus of 0.004mg R/kg and the infusion was increased by 0.02mg/kg until the therapeutic endpoint was reached. The infusion was then stopped and serial blood, urine and gastric fluid samples were obtained for the determination of R and GA during the next 12 hr. R was determined by HPLC. These values were used to calculate an IV dose which when administered every 6 hr would suppress GA $\geq 90\%$. On day 2 the calculated dose was given and the monitoring of R pharmacokinetics (PK) and GA were repeated. When C were eating the IV R was crossed over to oral R. Following repeat PK analysis the doses of R were individually adjusted to give a BID dose which would result in an average serum R concentration which suppressed GA $\geq 90\%$ in that patient. C were then discharged to receive that dose for 6 wks. The minimum effective serum R concentration was 22.6ng/ml (range 9-65ng/ml). PK analysis revealed ($\pm$ SD) t_{1/2}, 1.8(0.2)hr; Vd, 2.1(0.19)4kg; Clp, 724.3(163.7) ml/min/1.73m². The absolute bioavailability of R averaged 51% (range 35-95%). Minimal PK differences were observed comparing IV and oral dosing. These data suggest that 1) R is a potent inhibitor of GA in C; 2) C require greater R/kg than adults; 3) oral doses of R should be $\approx$ twice that of IV.

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ROLE OF CYCLIC 3',5'-ADENOSINE MONOPHOSPHATE (cAMP) IN SURFACTANT RELEASE FROM TYPE II EPITHELIAL CELLS. Ward R. Rice, William M. Hull, Jeffrey A. Whitsett, Children's Hospital, University of Cincinnati

Beta-adrenergic agonists enhance surfactant release, presumably by increasing synthesis of cAMP and activation of cAMP-dependent protein kinase. The present study compares the effect of terbutaline and forskolin on cAMP levels, protein kinase activation ratios, and surfactant release in isolated rat lung Type II epithelial cells in primary culture. Cytosolic cAMP levels rose significantly by 1 minute following exposure and persisted past 20 minutes:

	1 min.	3 min.	5 min.	20 min.
control (C)	.10 $\pm$.04	.11 $\pm$.04	.17 $\pm$.08	.09 $\pm$.03
terbutaline (T, 10 uM)	.19 $\pm$.08	.22 $\pm$.03	.25 $\pm$.06	.24 $\pm$.11
forskolin (F, 5 uM)	.45 $\pm$.16	.67 $\pm$.20	2.10 $\pm$.50	1.58 $\pm$.90
T plus F	1.49 $\pm$.09	4.60 $\pm$.21	>5.0	4.80 $\pm$ 1.4

$p < 0.05$ by analysis of variance for all groups compared to control; mean $\pm$ SEM of three experiments; fmols/100 ul. T plus F had a synergistic effect on cAMP levels. Protein kinase activation ratio increased in the presence of T+F from .45 $\pm$.03 for C to 0.85 $\pm$.05 for T+F. The effect of T and F on surfactant release was additive: C=0 $\pm$ 21%, T=18 $\pm$ 8%, F=258 $\pm$ 45%, T+F=412 $\pm$ 74% (mean $\pm$ SEM). Dose response curves resulted in EC50 values of 1 uM and 0.5 uM for T and F, respectively. Our results demonstrate a rise in cytosolic cAMP levels, increased protein kinase activation ratios, and subsequent surfactant release from isolated Type II cells, supporting a role for cAMP as a second messenger for stimulated surfactant release.