● 416 CEFTAZIDIME (CTZ) CLEARANCE (CL) WITH CONGENITAL URINARY TRACT OBSTRUCTION (UTO). Robert M. Ward, Mark F. Bellinger, Brent W. Snow, W. Manford Gooch, and Stan Davis. (Spon. by M. Simmons) Depts of Peds and Urol, Univ of Utah and Primary Children's Hospital, Salt Lake City, UT.; Dept of Surgery, Children's Hospital of Pittsburgh, Pittsburgh, PA.

Congenital UTO is the leading cause of childhood renal failure. Although these children receive complex drug therapy, the effects of UTO upon pharmacokinetics have not been adequately studied in immature humans or animals. Pseudomonas infections often complicate congenital UTO and may be treated with CTZ. To study the effects of UTO upon CTZ kinetics, we produced unilateral UTO in 3 fetal sheep at 75d/146d gestation. After spontaneous term birth, catheters were inserted to: drain the obstructed kidney; separately collect urine from the unobstructed kidney; and infuse drug and sample blood separately. Obstructed kidney glomerular filtration rates ranged from 0 to 28% of total by DTPA renal scans. CTZ was infused into 3 lambs for 3 hrs before 3 one hr urine collections to determine each kidney's: CTZ CL, creatinine CL (CR CL), and fractional sodium excretion (FENa). UTO decreased urine flow (0.05 to 0.01 ml/min·kg, p<.05); CR CL (2.16 to 0.44 ml/min·kg, p=.002); and increased FENa (0.35 to 7.94%, p<.05). UTO reduced urine [CTZ] to a low of 74.3±8.6 µg/ml. CTZ CL (y) correlated with CR CL (x) such that y=1.60 x -0.10 (r=.80, p<.001). UTO severely impairs renal function as well as CTZ excretion. Pseudomonas kidney infections in infants with bilateral UTO may require higher CTZ doses to reach therapeutic urine [CTZ] and longer dosing intervals which may be estimated from CR CL.

417 THE NEED FOR A LOADING DOSE OF GENTAMICIN (G) IN NEONATES. Kristi L. Watterberg, H. William Kelly (Spon. by John D. Johnson); University of New Mexico School of Medicine, Department of Pediatrics, Albuquerque

G often has a prolonged half life ($T_{1/2}$) in premature or sick newborns; therefore, modified G dosing schedules have been developed, with longer dosing intervals to accommodate increased $T_{1/2}$. Neonates also have wide variability in distribution volumes (Vd). In adults, early attainment of therapeutic levels of aminoglycosides has been correlated with positive outcome from gram negative sepsis. Neonates with large Vds may not achieve therapeutic peaks (5-10ug/ml) in the first 48° of therapy.

We studied 100 consecutive patients. G levels were drawn 1½°, 4° and 8° after a dose. Pharmacokinetic variables were calculated with a one-compartment open model. Results are mean±SD (GA=gestational age, BW=birthweight, Cl=clearance, PN=postnatal age).

GA	33.2±4.5wks (25-43)	$T_{1/2}$	7.95±3.57hrs (2.63-28.46)	Cl	50.3±19.3ml/kg/hr (13.4-165.0)
BW	1850±933gms (620-4635)	PN	4.4±5.0 days (0.1-25.0)	Vd	.542±.205 L/kg (.304-1.51)

In this population, 2.5mg/kg of G would result in an initial peak level of <5ug/ml in 45% of the patients. A loading dose of 4mg/kg would result in a peak of ≥5ug/ml in 92% of the patients and a peak of >12ug/ml in 7%. G toxicity appears to be related to high levels over time, whereas therapeutic efficacy may be related to adequate initial levels. We therefore recommend an initial G loading dose of 4mg/kg in newborns.

418 DIGOXIN AND DIGITOXIN CLEARANCE IN THE HUMAN FETUS. Carl P. Weiner and Marietta I.B. Thompson, Dept. Ob-Gyn, University of Iowa, Iowa City, IA. 52242. (SPON: J. Robillard).

In an accompanying abstract, we offer evidence that maternally administered digoxin does not readily cross the placenta of fetuses with cardiac disease. We have now administered digoxin and digitoxin to a fetus i.m. with supraventricular tachycardia in the late second trimester after maternally administered digoxin, verapamil, and procainamide failed. Fetal blood specimens were obtained by percutaneous umbilical blood sampling. Despite a sustained maternal digoxin concentration > 1.8 ng/ml, the maximum fetal digoxin (FD) was 0.86 ng/ml. 25 mcg of digoxin was placed into the fetal thigh q 8h x 3. The FD level 8h post load was below baseline. A reload of 50 mcg IM q 6h x 4 doses resulted in a FD of 1.51 ng/ml and a normal sinus rate. A second sample obtained 7.3h later was 1.1 ng/ml. The kel was calculated to be 0.0434h x 10-1 and the t 1/2 B was 15.9h. The Vd, estimated assuming a time 0 concentration of 1.9 ng/ml, was 487 ml/kg. Based on the Vd and clearance, a maintainance dose of 80 mcg q 12h was calculated to give a peak of 2.2 ng/ml and a trough of 1.4 ng/ml (actual measured trough was 1.2 ng/ml). In hopes of prolonging the dosing interval, we changed to digitoxin (DT). A 40 mcg load resulted in DT of 5.3 ng/ml and 2.9 ng/ml at 4.25h and 9.25h postdose. The calculated t 1/2 B was 5.8h. Serial measurement of fetal serum and amniotic fluid digoxin/digitoxin suggest some recirculation occurred. This is the first study of human fetal digoxin and digitoxin clearance in a continuing pregnancy after direct fetal administration. Our findings indicate that clearance is strikingly more rapid than in the newborn.

● 419 NITRENDIPINE (N) TREATMENT OF HYPERTENSION: ACUTE AND LONG TERM EFFECTS IN CHILDREN. Thomas G. Wells and Alan R. Sinaiko. University of Minnesota Hospital and Clinics. Depts. of Pediatric Clinical Pharmacology and Pediatric Nephrology, Mpls., MN.

Nitrendipine, a new long-acting calcium channel blocking agent, was used to treat hypertension in 8 children between 6 months and 17 years of age (mean=7.6±2.3 years). Seven of the children had renal disease and all subjects were previously treated with other antihypertensive agents. Systolic (SBP) and diastolic (DBP) blood pressure fell from a mean of 148 ±4/95±2 mmHg to 134±3/82±4 mmHg (p<0.02) one hour after an initial dose of 0.1 mg/kg. By 5 hours, SBP and DBP had fallen to 127±6/84±6 mmHg (p<0.05) in response to a total mean dose of 0.36 ±0.05 mg/kg. Seven of eight patients were continued on chronic N therapy. Long term data from these patients is as follows:

Duration of treatment	# of Patients	Dose of N (mg/kg/24hr)	SBP (mmHg)	DBP (mmHg)
Baseline	7	-	149±4	95±2
24 hr	7	0.74±0.11	131±4**	81±3**
7 days	7	0.94±0.11	119±6**	74±4**
2 weeks	5	1.19±0.27	123±7	72±5*
4 weeks	6	1.13±0.24	115±6**	72±7*
8 weeks	5	1.14±0.29	118±4*	78±9*

All data presented as mean ± SEM;
*: p<.05; **: p<.01 cf baseline values.

No significant changes in total or ionized calcium, BUN, or creatinine were noted. No adverse effects were observed. These data suggest that N is an effective agent for long term antihypertensive therapy in children.

ENDOCRINOLOGY

420 CONGENITAL CONDITIONS ASSOCIATED WITH PERMANENT INFANTILE HYPOTHYROIDISM, N.E. Congenital Hypothyroidism Collaborative, Dartmouth Medical School, Dept of Mat/Child Health. Banforth et al have reported that among 37 patients with infantile hypothyroidism diagnosed as a result of screening, 7 had other congenital anomalies. We reviewed the records of 190 patients similarly diagnosed in N.E. in 1976 through 1981. Adequate information was available for 181 infants. We are reviewing a second cohort born in the ensuing 5 years. The incidence of congenital conditions was not significantly different from the accepted incidence of 3% in the general population. The congenital anomalies and other associated conditions (some of which were manifested only years after birth) included: mild pulmonic stenosis (n=2), atrial septal defect, imperforate anus, Pierre Robin syndrome, familial microcephaly, patent ductus arteriosus, club foot, vertex cutis aplasia, Williams syndrome, late 21-hydroxylase deficiency, Trisomy 21 (n=2), and spastic di or hemiplegia (n=3). The association of permanent and transient hypothyroidism with Down syndrome is well known. No hypothyroid patients have as yet been recognized to have Turner syndrome. The instance of cerebral palsy is interesting because of its occurrence in certain endemic cretins. Again because of the small number of hypothyroid patients the incidence cannot be distinguished from that in the general population (1:250). The patient with 21-hydroxylase deficiency has dyshormonogenesis. Her euthyroid twin also has the hydroxylase deficiency. Three of the other patients with associated congenital conditions also have dyshormonogenesis. One of the patients with pulmonic stenosis has an euthyroid twin.

● 421 PRELIMINARY REPORT ON PATIENTS WITH INFANTILE HYPOTHYROIDISM AFTER THE THIRD GRADE. NE Cong. Hypothyroidism Collaborative, Dartmouth Medical School, Dept. Mat/Child Health. Our first 26 hypothyroid patients to complete the third grade were tested for IQ, school achievement, and various neuropsychologic functions. Their results were compared to those of 44 age and sex matched classmates. Their rates of progress and difficulties in school were compared to those of 36 siblings. Because it has been iterated in the literature that patients with infantile hypothyroidism, even with normal IQs, have school learning problems, the correlation of IQ with school achievement test scores was analyzed for the patients and their classmates. All testing was conducted during the summer vacation. The patients repeated fewer grades by the end of 3 grades than had their siblings. The same percentage of patients and siblings required special help at school such as tutoring, use of resource room, or special education classes. No significant difference in test results or correlation of IQ and achievement scores was found comparing patients and appropriate controls. The mean and SEM for IQ of the patients and of their classmates were 109.2 ± 2.1 v 110.9 ± 1.8. The Peabody Achievement Test scores expressed as grade achieved minus grade placement were: math 1.4 ± .08 v 1.3 ± .06, reading recognition 1.5 ± .07 v 1.4 ± .06, reading comprehension 1.4 ± .07 v 1.5 ± .05, spelling 1.4 ± .07 v 1.4 ± .07, general information 1.3 ± .06 v 1.4 ± .05. The examiners were unaware of the identity of the subjects. Unless a patient or mother mentioned previous testing in the study, the reliability of the examiners in identifying the patients was no greater than chance.