● 347 PREMEDICATION--AN UNAPPRECIATED RISK OF CT SCANS IN CHILDREN.

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Although consideration of risks associated with CT scans generally focuses on the effects of radiation and contrast agents, we have identified premedication as an additional risk among infants and children who undergo CT scans. As part of an intensive Pediatric Drug Surveillance (PeDS) Program, we evaluated adverse drug reactions (ADR) attributed to medications given prior to CT scanning to sedate 100 infants and children (ages 2 days to 16 yrs). ADR's attributed to premedication were observed in 12 patients (12%); 6 were of major severity, 4 were moderate and 2 were minor. Life-threatening cardiorespiratory depression/arrest occurred in 3 patients after meperidine, meperidine plus diazepam and morphine. Other reactions were CNS depression, behavior changes, voiding problems, respiratory compromise and vomiting. Premedications implicated were morphine, meperidine, promethazine, chlorpromazine, chloral hydrate and diazepam. The risk of an ADR was not materially affected by admission diagnosis or prior receipt of CNS depressants, but ADR risk was increased among older patients (5+ yrs.), when > 3 premedications were used and when doses were higher than recommended. These observations suggest that ADR's to premedications must be considered when assessing the risk of CT scans in children, and that greater attention be paid to developing appropriate CT scan premedication regimens.

348 ONTOGENY OF THE β-ADRENERGIC RECEPTOR IN RABBIT PLACENTA.

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β-Adrenergic stimulation of the placenta causes increased glycogenolysis and cAMP production. These effects are presumably mediated through the β-adrenergic receptor (βAR). In this study the βAR in rabbit placenta was characterized and shown to increase with gestational age. Binding of the β-adrenergic antagonist dihydroalprenolol, (-)[^{3}H]DHA, to rabbit placental membranes was saturable to a single class of sites, K_D=1.67± .07(nM), n=11 and Bmax=326±33 fmoles/mg. Agonist competition for the βAR was performed in the presence of the non-hydrolyzable GTP analog Gpp(NH)p (required for Hill coefficient = 1) and showed the potency order (-)iso >> (-)epi > (-)norepi characteristic of the β_2 subtype. However, competition experiments with subtype specific agents metoprolol (β_1) and zinterol (β_2) indicated that the rabbit placenta contained approximately equal populations of βAR subtypes (51% β_1, 49% β_2). Rabbit placenta βAR/DNA increased 5.3 fold from day 16 to day 27 of gestation (410±120 fmoles/mg DNA to 2184±354 p<.001). During this interval protein/DNA (25±1.8mg/mg DNA to 34.2± 4.1) and DNA (4.0±.2mg/gm tissue to 3.5±.2) changed less markedly. K_D did not change with gestation. (-)[^{3}H]DHA binding was coupled with catecholamine stimulated adenylate cyclase (1.5 fold stimulation, p<.01). Rabbit placenta has two βAR (β_1 and β_2) in high density coupled to adenylate cyclase. Maximal βAR density occurs in late gestation coincident with the known catecholamine surge in fetal rodents suggesting a regulatory role for catecholamines in placental metabolism.

349 EFFECT OF INTRAVENOUS (IV) INFUSION METHODS ON AVAILABILITY OF CHLORAMPHENICOL (C) AND ITS SUCCINATE ESTER (CS)

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The rate of IV drug delivery is affected by many factors including characteristics of the drug, IV flow rate, and site of injection into the system. Because of the frequent use of CS in pediatric patients, we examined the rate of CS delivery from a standard pediatric IV infusion set (Buretrol^R-Travenol). Using 3 flow rates, and 3 injection sites (buretrol, y site, flashball), timed samples of the IV fluid delivered from the set were collected for 6 hr and analyzed for CS by an HPLC method. We found large differences in the delivery time (min) for 95% of the injected CS:

Site	flow rate (ml/hr):	29	15	5	
flashball		30	58	180	Time
y site		70	130	360	(min)
buretrol		150	280	>360	

To assess the clinical significance of these differences, CS and C steady state serum concentrations (6 samples over 6 hr; measured by HPLC) were studied in fifteen patients (age 0.2-15 yr) receiving CS, 25 mg/kg, injected into the buretrol and flashball on consecutive days. Flashball injections resulted in higher peak CS conc (p<0.001) and peak C conc (p<0.005) in a shorter time from the start of infusion (p<0.005). At flow rates >7 ml/hr, trough conc and area under the curve were similar with the two sites. These data show the importance of defining IV flow rates and drug injection sites when monitoring single serum CS or C conc or when calculating kinetic parameters.

● 350 KINETICS OF CHLORAMPHENICOL (C) AND ITS SUCCINATE ESTER (CS) IN PEDIATRIC PATIENTS.

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CS must be hydrolyzed to C to provide antimicrobial activity. A thorough knowledge of CS disposition is needed to understand C kinetics in children. Thirty patients (age 1.5 wk-17 yr) were studied to characterize CS and C kinetics. CS, 25 mg/kg was administered every 6 hr intravenously over 0.5 hr. At steady state, blood samples were obtained at 0, 0.5, 1, 2, 4 and 6 hr after starting the infusion. In 10 patients, all urine was collected over the same 6 hr. CS and C concentrations (conc) were measured by an HPLC method. Peak serum CS conc ranged from 7.38-79.5 mcg/ml and peak C conc from 9.3-66.21 mcg/ml. A rapid decline in serum CS conc was followed by a slow elimination phase in half of the patients. CS was still detectable in serum at 4 hr in 10 patients and 6 hr in 9 patients. Disposition of both CS and C appeared to be a first order process. Half-life of CS ranged from 0.3-5.5 hr and of C from 1.6-7.9 hr. Total body clearance of CS ranged from 0.152-3.27 L/kg/hr and of C from 0.043-0.425 L/kg/hr. 5-25% of the total dose of CS was excreted in the urine as either C (2-7%) or CS (3-18%). These data suggest that CS kinetics may be characterized by a two compartment open model. Its hydrolysis is not instantaneous but more variable than previously appreciated. These factors may account for the large variability in C kinetics found in our study and described in previous reports of C pharmacokinetics in children.

● 351 FUROSEMIDE PHARMACOKINETICS AND DRUG RENAL EXCRETION IN PREMATURE INFANTS ON CHRONIC THERAPY

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During the treatment of 12 normally hydrated prematures with furosemide (F) for chronic lung disease (BPD) F serum levels and urine excretion were measured using gas chromatography. Six hours post drug administration the diuretic response was monitored in treated group (TG) and compared to the control group (CG) of 10 premature infants. The mean gestational age of TG was 29 weeks (range 26-31) and of CG was 30 weeks (range 27-36). The TG received a single bolus IV dose of F (1mgm/kg/day) daily for 4 to 7 days. Eight patients entered the study on day 7, and 4 patients were 9-11 days old on entry. Duration of the study was 4-7 days. The mean renal clearance of F on day 1(D1) of the study was 0.04 cc/min (range 0.003cc/min to 0.13cc/min). The mean renal clearance after 4(D4) or 7(D7) days of therapy was 0.05cc/min (range 0.003cc/min to 0.12cc/min). On D1 mean serum F levels were 4.6 ugm/ml at 2 hours and 3.66 ugm/ml at 6 hours after F. On D4 and D7 the mean serum levels were 10.33 ugm/ml (2 hrs) and 6.67 ugm/ml (6 hrs). This is a significant increase in mean serum levels ($P \leq .01$) from first day of treatment. 6 hour plasma half life ($T_{\frac{1}{2}}$) in these patients changed from mean of 5.2 hours (D1) to 10 hours (D4 or D7). In 2 patients mean $T_{\frac{1}{2}}$ over 12 to 24 hours was 7.15 hours (D1) and increased to 26.15 hours. Mean urine volume during 6 hours in TG was 33.9±21 ml and in CG was 25.3±13 ml (p=.35NS). Six hour sodium excretion was 1.76 mEq (TG) and 1.45 mEq (CG). During daily F administration, there is serum drug accumulation due to the very low renal clearance.

● 352 POSTNATAL DEVELOPMENT OF α_1 ADRENERGIC RECEPTORS IN THE RAT HEART.

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Myocardial contractility is mediated by both α and β adrenergic stimuli. α-Adrenergic agonist increases inotropic response independently of c-AMP and is thought to involve primarily α_1 adrenergic receptor (α_1AR) subtype present at postsynaptic receptor sites in the heart. Since sympathetic innervation of rodent myocardium develops postnatally it is also likely that developmental changes occur in the postsynaptic receptor sites. Thus we measured postnatal development of α_1 and β adrenergic receptors(βAR) in rat myocardium by binding experiments with ^{3}H-prazosin and ^{3}H-dihydroalprenolol (^{3}H-DHA). ^{3}H-Prazosin and ^{3}H-DHA binding to rat ventricular membranes were rapid, saturable, stereospecific and reversible. The competition for ^{3}H-Prazosin by agonists was in the order of Epinephrine= Norepinephrine>>Isoproterenol and that for ^{3}H-DHA was Isop>>Epi=Norepi. The competition for ^{3}H-Prazosin by antagonists was in the order of Prazosin>WB401>phentolamine>>Yohibimine and did not vary with age. The numbers of α_1AR and βAR sites in rat ventricular myocardium were:

	1 Day	5 Day	15 Day	28 Day	Adult	K_D
α_1(^{3}H-Prazosin)	35±9	121±10	163±5	101±5	83±5	0.2nM
β (^{3}H-DHA)	61±6	52±3	50±1	48±3	37±4	2.0nM

M±S.E. femtomoles·mg^{-1} membrane protein, n = 4 at each age

There was no change in K_D (affinity) with age for either ligand. We conclude that the number of myocardial α_1AR increases rapidly after birth in rat myocardium and that the pattern is distinct from that of βAR. We speculate that the postnatal development of α_1AR and βAR is independently regulated in rat myocardium and that α_1AR are likely to be linked with postnatal neurosynaptic development while βAR are not.