Eugenio Cefali, Wesley J. Poynor, Lorne K. Garrettson; Pharmacokinetic Modeling of Lead During EDTA Therapy, Virginia Commonwealth Univ., Medical College of VA Hospitals, Schools of Pharmacy and Medicine, Richmond, Virginia.

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Mathematical simulation models for lead distribution in the body have been developed from studies of tracer lead administration to adults. These models do not predict the rebound of blood lead usually seen following chelation with EDTA. Children with elevated BLL were followed with daily blood assays during and for 6 days after chelation with EDTA, 50 mg/kg/d.

Using a published model, a successful fit was accomplished only with increases in the size, and transfer rates of lead into and out, of shallow compartments. Initial conditions were determined by adjusting intake to mimic the observed BLL curve prior to reaching prechelation levels in selected patients. The model was constrained to fit the observed urine lead elimination during chelation. The deep compartment, (presumably cortical bone), is so deep, in pharmacokinetic terms, that it is not important to the rebound phenomena.

Partial validation of our model will come if it continues to predict clinical response to EDTA. More effective chelation therapy is the major utility of such models.

THE EFFECT OF PGE_1, $PGF_{2\alpha}$ AND PGI_2 ON CEREBRAL BLOOD FLOW (CBF) AND OXYGEN METABOLISM ($CRMO_2$) OF THE NEWBORN (NB) PIGLET, WITH AND WITHOUT INDOMETHACIN (Id) PRE-TREATMENT. S Chemtob, N Laudignon, K Beharry, J Rex, JV Aranda. Dept of Dev Pharm and Ther, Montreal Children's Hosp., McGill University, Canada.

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A role for PGs in the regulation of CBF of the NB has been ascribed only through indirect evidence. We evaluated the effects of incremental doses of PGE_1 (doses: 0, 10^{-7}, 10^{-6}, 10^{-5} g/kg), $PGF_{2\alpha}$ and PGI_2 (doses: 0, 10^{-8}, 10^{-7}, 10^{-6} g/kg) q 20 min, with and without Id pre-treatment, on CBF (radiolabelled microsphere technique) and $CRMO_2$ of 1-3 day old awake piglets. Total CBF is presented. Similar changes were seen for the eyes and 13 brain regions. Blood gases, aortic pressure and cardiac output remained stable. PGE_1 doses of 10^{-7} g/kg decreased CBF by 30 %, and 10^{-5} g/kg increased CBF by 39.5 % (n=6). $PGF_{2\alpha}$ (10^{-6} g/kg) (n=8), a potent adult cerebral vasoconstrictor, and PGI_2 (10^{-7} g/kg) (n=6) increased CBF, ($P < 0.05$ and $P < 0.01$, respectively). Id (3 mg/kg IV, 5 mins post baseline CBF determination) decreased CBF by 38 % ($P < 0.02$; n=6). Only PGI_2 (10^{-8} and 10^{-7} g/kg) reversed (partially) the CBF decrease induced by Id ($P < 0.04$; n=6). CBF did not change in 7 controls. $CRMO_2$ correlated with CBF in all groups ($r = 0.69$-0.87, $P < 0.0001$), except for PGI_2. The findings imply that: 1) Ontogenic changes in receptor binding or population, and/or post-receptor events may explain the opposite CBF responses to $PGF_{2\alpha}$ in the NB and adult; 2) In the presence of elevated perinatal PG plasma levels, the NB is devoid of local cerebrovascular constrictor PG, possibly contributing to its narrow CBF autoregulatory range.

ALKALOIDAL COCAINE ("CRACK") IN PREGNANCY: A PROSPECTIVE COHORT STUDY. Radha Cherukuri, Howard Minkoff, Aruna Parekh, Joseph Feldman, Leonard Glass. Departments of Pediatrics and Obstetrics, SUNY/H.S.C., Brooklyn, NY.

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Twenty-five women who used crack during pregnancy were compared to a cohort group of non crack using women matched for age, socioeconomic status, parity, presence or absence of prenatal care and use of tobacco and alcohol. Crack exposed infants were eight times more likely to weigh less than 2.5 kg than infants of cohort mothers. There was a higher frequency of head circumference less than the tenth percentile for gestational age ($p<0.025$) in the study group infants, and mean gestational age in this group (37.5±3.8 weeks) was significantly lower than in the cohort infants (39.3±2.1 weeks; $p=0.027$). There was a higher frequency of premature rupture of membranes ($p=0.046$) in the crack than in the cohort group. Fifty-five percent of infants exposed to crack in-utero had abnormal neuromuscular symptoms, usually of short duration.

These studies suggest that use of crack has a deleterious effect on the outcome of pregnancy, and that careful medical follow-up of these infants is necessary.

LONG TERM FETAL INDOMETHACIN EXPOSURE AND NEONATAL OUTCOME. P.A.DeGiulio, S.Abbasi, A.G.Gerson, A.Johnson, G.Kaur & R.Bolognese. Spon. by Lois H. Johnson. Univ of PA Sch of Med, Pennsylvania Hosp, Newborn Pediatrics & Perinatology, Philadelphia, PA.

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Animal studies and isolated human case reports have raised concerns about the possible premature closure of the ductus arteriosus (PDA) and pulmonary hypertension (PPHN) in the fetus exposed to indomethacin (indo). Although short term (<48 hrs) indo use for premature labor has been shown to be safe in humans, the side effects of long term (>48 hrs) use have not been well documented. The clinical course of 249 neonates during a 2 year period who were exposed in utero to tocolytic agents was evaluated. 24 pregnant women in preterm labor and failing parenteral tocolytics had indo added to their regimen (200-300 mg/day). Indo was continued until 33 wks. These infants were compared to those who received other tocolytic agents (control). Mean ±SD values for gestational age (GA,wks), duration of tocolytic exposure (Toco, wks), time in utero gained (TG, wks), PPHN, PDA, respiratory distress (RDS), infant mortality (Mort) for indo and control are:

	GA	Toco	TG	PPHN	PDA	RDS	Mort
Indo	32 ±3.4	5.7 ±4.7	6.7 ±5.7	2	5	15	2
Control	36 ±2.7	4.7 ±4.7	5.2 ±4.9	1	5	19	0

There was no difference between indo (n=30) and control babies (n=219) when matched by GA for BW, RDS, apnea, IVH or PDA. Conclusions: 1. The addition of indo in pregnancies complicated by preterm labor resistant to standard therapy prolonged gestation. 2. There was no significant risk of RDS, apnea, IVH or PDA in long term indo exposure prior to 33 wks gestation. 3. Sample size prevented risk analysis of PPHN, BPD, and mortality.

EFFECTS OF OXOTREMORINE AND ACETYLCHOLINE ON ELECTROPHYSIOLOGIC PROPERTIES OF THE FETAL HEART. Denis DiLallo and Peter Danilo (Spon. by L.S. James) Depts. of Pharmacology and Pediatrics, Columbia University, NY, NY

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We determined the relative effects of acetylcholine (ACh) and oxotremorine (Oxo) on sino-atrial and atrioventricular nodal function in the fetal heart. Oxo is a cholinesterase-resistant agonist. Hearts from fetal guinea pigs in the last trimester were perfused retrogradely through their coronary vasculature with a physiologic salt solution containing ACh or Oxo, $1x10^{-8}$ to $2.5x10^{-7}$M. We measured sino-atrial (SA) rate; atrioventricular conduction time (AVCT); and the Wenckebach cycle length (WBCL), the shortest paced cycle length resulting in 1:1 AV conduction. Control values were ($\bar{X}$±SE, n=8):SA rate, 196±15 beats per min; AVCT, 81±3 msec; WBCL, 208±11 msec. Both ACh and Oxo induced concentration dependent, reversible changes in all 3 variables. Maximum effects of ACh occurred at $2.5x10^{-7}$M; those of Oxo between $1x10^{-8}$ and $5x10^{-8}$M. Maximum percent change, compared to control, of ACh and Oxo were, respectively, -28±3% and -51±7% for SA rate ($p<.01$); +10±6% and +23±2% for AVCT ($p<.02$); and +34±9% and +114±48% ($p<.02$) for WBCL. These data indicate that Oxo is a more potent agonist than ACh with respect to its electrophysiologic effects on the fetal heart. These differences may result from a relatively high cholinesterase activity which attenuates the action of ACh but not of Oxo.

THE ADVANTAGE OF STABLE ISOTOPE LABELED THEOPHYLLINE FOR STEADY STATE KINETICS IN PREMATURE INFANTS. C. Dothey, K. King, S. Kaw, K. Y. Tserng, CWRU at Cleveland Metro. Gen. Hosp. and V. A. Hosp., Cleveland, OH: SUNY at Stony Brook, Schneider Children Hosp., New Hyde Park, N.Y.

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Theophylline (TH) disposition is known to very greatly in the neonatal period. Parameters obtained after discontinuation of the drug or after single dose study yield misleading information if the drug has dose-dependent kinetics. Therefore, pharmacokinetic parameters are commonly determined between dosing intervals once steady state has been achieved. The purpose of this study was to evaluate the accuracy of the "in between doses" method in the neonatal population treated with TH. Nine preterm infants (GA:26-30wk, postnatal age; 7-191d, study weight:0.910-1.830kg) received one pulsed dose of stable isotope labeled theophylline TH-3 (1,2 15N, 2 13TH), given IV. Blood and urine were collected for one week. All samples were analysed by selected ion monitoring GC/MS. Pharmacokinetic parameters determined from TH decay during one 8h dosing interval were compared to those obtained from the disappearance curve of TH-3 over one week period. Systemic clearances calculated from AUC indicated that TH and TH-3 disposition were identical. (paired T test:N.S.) However, TH-3 t1/2 (28.7±14.5h) was significantly longer than TH t1/2 (14.8±6h). The difference cannot be accounted for by a distribution phase since TH t1/2 was calculated 8-16h after the previous dose. Urine data showed an increased excretion of TH following each dose as a result of a diuretic effect. Therefore, the shorter t1/2 obtained from the multiple-dose method reflects a fast decay due to diuresis, while the longer t1/2 obtained from the stable isotope method is the real half-life. We conclude that calculating theophylline half-life between two doses, significantly underestimates the real t1/2 representing potential risk of toxicity.