409 *METHYLPARABEN(MP) CONCENTRATION IN WHOLE BLOOD FOLLOWING GENTAMICIN ADMINISTRATION IN PREMATURE INFANTS.* *Gary Rockwell,Wilmer Stratton,Scott Chavat,and Peter Uden.(Spon. by Edward Reiter).Baystate Medical Center, Dept. of Pediatrics,Spfld.,MA,Univ. of Mass.,Dept. of Chem.,Amherst, MA*

A preservative, benzyl alcohol, has been demonstrated to accumulate to potentially toxic levels in preterm infants. Subsequently, use of benzyl alcohol has been curtailed. Parabens are also preservatives which find wide application in the food,cosmetic, and pharmaceutical industries. However, parabens have not been quantitated when given with other medications,such as gentamicin. The methyl ester of parahydroxybenzoic acid(MP), if present in sufficient concentration,may displace bilirubin from albumin.

A high pressure liquid chromatography technique was developed to measure MP in small(0.5ml) blood samples. MP was measured prior to and 1 hr. after an IM dose of gentamicin sulfate in prematures already receiving antibiotics. MP was present at a concentration of 1.8mg/ml in this gentamicin preparation. The mean concentration of .23µg/ml pre-injection was not significantly different from a post-injection average concentration of .31µg/ml (n=8).The highest concentration observed(.73µg/ml) is two orders of magnitude lower than that felt to be toxic for benzyl alcohol.

BW	*GA*	*Pre*	*Post*
Mean=1.596kg	*31.5 weeks*	*.23µg/ml*	*.31µg/ml*
Range (1.021-2.169)	*(27-36)*	*(.00-.58)*	*(.09-.73)*

No significant difference was found between means using a one tailed t test. Non-accumulation with hepatic and renal compromise has yet to be demonstrated.

410 PREGNANT COCAINE ABUSERS AND THEIR INFANTS. Tove S. Rosen and Helen L. Johnson(Spon. by L.S.James) Coll. of P&S, Columbia U., Presby.Med.Ctr.,DeptPed,NY

Cocaine (C) abuse is a major public health problem. To study the effects of C abuse on the course of pregnancy and infant development, we have been following 2 groups of pregnant women; one on C and one drug-free. The data were analyzed in 3 groups: GP1, drug-free; GP2, methadone maintenance(M) and C abuse; GP3, C used in combination with marijuana and/or alcohol. For all findings reported, $p<.05$. GPs 2&3 commenced prenatal care later, with less frequent clinic visits and less adequate nutrition. Beer consumption was higher in GP2; hard liquor intake in GP3. C abuse was similar in both groups, but marijuana abuse was greater in GP3. Drug abuse decreased as gestation progressed.

There were no differences in the incidence of perinatal complications, 5min. Apgar score, or gestational age. However, mean birthweight, head circumference(HC), and length(L) were significantly smaller in GP2. Mild to moderate withdrawal symptoms occurred in 73% of GP2 and 25% of GP3. Neonatal course was similar in all groups. Infants with an uncomplicated course were enrolled in follow-up. At 6 mo., GP2 again demonstrated smaller weight, HC, and L, and more frequent hypertonicity and irritability.The groups did not differ on the Bayley Scales or any other variables.

In conclusion, C abusers comprise a high risk group during pregnancy, with frequent multidrug abuse and poor nutrition. The infants of mothers on both M and C appear to be at greatest risk for low weight, HC, and L from birth through 6 mo. While infants of C abusers did not differ from controls in growth and development, only further follow-up will show if any longterm effects occur.

† **411** HEMODYNAMIC EFFECTS AND MARGIN-OF-SAFETY OF ISOFLURANE IN NEWBORN PIGLETS. Richard A. Schieber, D. Ryan Cook, Gerald K. Shiu, Richard A. Orr (Spon. by William H. Neches), Univ. of Pittsburgh School of Med. and Children's Hosp. of Pittsburgh, Depts. of Anesthesia and Pediatrics, Pittsburgh, PA

Isoflurane (ISO), a potent inhalation anesthetic, is commonly used for infant anesthesia, but its cardiovascular effects are poorly defined. We invasively measured the effects of ISO on the major determinants of cardiac output in 15 acutely-instrumented healthy newborn piglets and 9 age-matched controls. End-tidal ISO concentrations were determined by mass spectrometry. Hemodynamic readings were obtained at baseline, 0.5, 1.0, and 1.3 MAC (minimum alveolar concentration needed for anesthesia).

At 1 MAC: CI -5% (NS), MAP -37%*, systemic resistance -32%*, dP/dT/DP40 -32%*, echo shortening fraction -20%*, HR -15% (NS), LVEDP -18% (NS). 1.3 MAC ISO did not depress any variable further, except HR (-19%*) (*=$p<.05$ vs baseline and control). 5 pigs who had ↓ HR were paced; MAP, dP/dT/DP40, and systemic resistance remained low while CI did not change. In 12 other piglets, the blood, heart, and brainstem lethal:MAC concentration ratio was 2.1, 2.0, and 2.8, respectively.

At 1 MAC, ISO depressed contractility and occasionally caused bradycardia. Because MAP and systemic resistance decreased to a similar extent, CI was unchanged. ↓ MAP may adversely affect flow to those vital organs lacking mature autoregulation. ISO has a limited margin-of-safety in newborn piglets.

● **412** HEMODYNAMIC AND PHARMACODYNAMIC EFFECTS OF HIGH-DOSE FENTANYL ON NEWBORN PIGLETS. Richard A. Schieber, Richard L. Stiller, D. Ryan Cook (Spon. by William H. Neches), Univ. of Pittsburgh School of Med. and Children's Hosp. of Pittsburgh, Depts. of Anesthesia, Pediatrics, and Pharmacology, Pittsburgh, PA

High-dose fentanyl is used for intra- and postoperative newborn cardiac anesthesia, yet its pharmacodynamic effects on the major determinants of cardiac output in the newborn are unknown. We studied 25 acutely-instrumented healthy piglets < 2 wks old; 5 received 50 µg/kg IV fentanyl (F), 5 controls received only 0.01-0.03 mg/kg IV atropine (A) to fix HR, and 9 received both (F/A). F pharmacokinetics were studied in 6 others.

Mean plasma F concentrations were 25.4, 12.7, and 7.9 ng/ml at 5, 15, and 30 min, respectively. $T_{½}(\alpha)$=2.1 min and $T_{½}(\beta)$= 35.8 min. Piglets given only F had their maximum hemodynamic changes from baseline at 5 min: MAP +42%, CI -42% (thermodilution), HR -36%, LVEDP +81%, and TPRI +93% ($p<.05$ vs baseline for each variable). The degree of change correlated well with the log F concentration ($r=.98$, $p<.05$). In F pigs, contractility (LV peak dP/dT and echo shortening fraction) did not change. However, piglets given F/A had no significant hemodynamic changes from baseline, other than a 14% increase in MAP, and were statistically similar to the control group given A alone.

Fentanyl, when given alone, had adverse effects on newborn piglets, but fentanyl with atropine did not alter normal hemodynamics during the first elimination half-life. The use of fentanyl is recommended for newborns provided a vagolytic agent is used concomitantly.

413 SUFENTANIL: PHARMACOKINETIC AND HEMODYNAMIC PROPERTIES OF A NEW NARCOTIC. Richard A. Schieber, Richard L. Stiller, D. Ryan Cook (Spon. by William H. Neches) Univ. of Pittsburgh School of Med. and the Children's Hosp. of Pittsburgh, Depts. of Anesthesia, Pediatrics and Pharmacology, Pittsburgh, PA

Sufentanil (SUF) is a potent narcotic recently approved for use in adult cardiac anesthesia. Its hemodynamic and pharmacokinetic properties are untested in newborns. We measured plasma SUF concentrations by radioimmunoassay in 7 healthy newborn piglets given 15 µg/kg SUF by IV bolus. Its effects on the determinants of cardiac output were invasively measured in 6 piglets.

Plasma SUF conc. fit a 3-compartment model; $T_{½}(\alpha)$=2.0 min and $T_{½}(\beta)$=39.7 min. Cardiac effects were compared with baseline:

	5 Min	15 Min	30 Min	45 Min	60 Min
HR	-15%	-6%	-2%	+2%	+15%
MAP	+16%	+11%	+15%	+11%	+9%
CI (thermodilution)	-26%*	-16%*	-23%*	-29%*	-32%*
Systemic Resistance	+58%*	+28%*	+49%*	+60%*	+69%*
LV dP/dT	+6%	+19%*	+28%*	+19%*	+36%*
LVEDP	+68%	+16%	-46%	-78%	-73%

*$p<.05$ vs baseline by repeated measures analysis

The α and β-phase half-lives of SUF and fentanyl (another potent narcotic) are similar in the piglet. Unlike fentanyl, SUF does not affect MAP or HR. CI is depressed less by SUF, perhaps because it increases contractility. Both drugs increase afterload. SUF does not affect preload significantly. Because SUF has a positive inotropic effect with minimal adverse hemodynamic effects on newborn piglets, it merits a clinical trial in newborn cardiac anesthesia.

● **414** PHARMACOKINETIC BASIS FOR ANTENATAL DOSING OF PHENOBARBITAL FOR THE PREVENTION OF NEONATAL INTRACEREBRAL HEMORRHAGE. Seetha Shankaran, Eugene Cepeda, Nestor Ilagan, Ralph Kauffman. Wayne State Univ. Sch. of Med, Children's Hosp of Mich., Dept. of Ped., Detroit, MI.

Transplacental and elimination pharmacokinetics of phenobarbital (PB) were analyzed in pregnant women and their neonates with the aim of determining the dose to be administered to pregnant women to achieve levels in the neonate for prevention of neonatal intracerebral hemorrhage (ICH). A single PB dose of 500 mg was selected to achieve a serum concentration of 10 µg/mL in the women according to the equation: dose (mg/Kg) = serum conc (µg/mL) x Vd (L/Kg); assuming average weight to be 50 Kg and Vd = 1.0 L/Kg. Twenty-five women in premature labor <35 wks gestation received 500 mg PB administered intravenously over 30 min. Average weight of the women was 69.1 ± 13.5 Kg (all values mean ± SD); the actual mean dose of PB therefore was 7.5 ± 1.4 mg/Kg. The mean time from PB administration to delivery was 5.6 ± 4.6 hrs (range 16 min. to 17 hrs). The maternal serum PB level at delivery was 8.8 ± 1.2 µg/mL and the cord serum level was 9.0 ± 1.8 µg/mL. There was no correlation between the time from PB administration to delivery and the cord:maternal serum concentration ratio. This indicated transplacental equilibration within 16 min. of maternal dosing. Mean apparent $t_{½}$ of PB estimated in 11 infants was 175.5 ± 45.6 hrs; this is comparable with $t_{½}$ in neonates receiving PB postnatally. Based on this study, we recommend a 10 mg/Kg dose of PB for the pregnant woman to achieve a level of 10 µg/mL. This level has been found to be protective against ICH (Shankaran et al, Ann Neurol Abstr #14, 1984).