Title: MATERNAL AND FETAL UPTAKE OF BUPIVACAINE vs. LIDOCAINE AT STEADY STATE PLASMA DRUG CONCENTRATIONS.

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Introduction. In our previous study, involving a constant rate intravenous infusion of lidocaine (0.1 mg/kg/min) to pregnant ewes, maternal clearance, placental transfer, and maternal and fetal tissue distribution of the drug were determined under steady-state conditions (1). Data obtained from a similar study infusing bupivacaine are presented here, and compared with those following lidocaine infusion.

Materials and Methods. Nine chronically instrumented pregnant sheep and their fetuses were studied at a mean (± SE) gestational age of 135 ± 2 days (term 148 days). Under spinal anesthesia catheters were placed in the mother's abdominal aorta and inferior vena cava. A hysterotomy was then performed and the fetal abdominal aorta and inferior vena cava were cannulated. Animals were allowed to recover for 3 to 4 days. On the day of study, after a control period, mothers received a constant rate intravenous infusion of bupivacaine, 0.025 mg/kg/min over 300 min (approximately 5 times the elimination half-life of the drug, previously determined from single bolus injections). Maternal and fetal arterial samples were obtained prior to and during the infusion, and plasma separated and frozen until drug analysis. Maternal and fetal blood pressure and heart rate were monitored throughout the experiment and recorded on a polygraph; arterial pH and blood gas tensions were determined intermittently. Fetal cardiac output was measured using radionuclide-labelled microspheres injected before and at the end of bupivacaine infusion. Thereafter, both mother and fetus were killed by an overdose of pentobarbital, and several organs removed and frozen. Bupivacaine analyses in blood and tissue samples were carried out using a gas chromatographic method. ANOVA and Student's t test were used for statistical analyses. $p < 0.05$ was considered significant.

Results. All mothers and fetuses were in healthy condition prior to and during the study (Table 1).

Table 1

	Pre-infusion	End of infusion
Mother		
pHa	7.47 ± 0.01	7.49 ± 0.01
$PaCO_2$ (mmHg)	30 ± 2	29 ± 2
PaO_2 (mmHg)	91 ± 3	97 ± 4
HR (b.p.m.)	108 ± 8	91 ± 5
MABP (mmHG)	81 ± 2	82 ± 2
Fetus		
pHa	7.36 ± 0.01	7.36 ± 0.01
$PaCO_2$ (mmHg)	42 ± 1	43 ± 2
PaO_2 (mmHg)	22 ± 1	22 ± 1
HR (b.p.m.)	146 ± 11	138 ± 17
MABP (mmHg)	57 ± 3	59 ± 4
CO (ml/min/kg)	451 ± 50	511 ± 38

Bupivacaine concentrations in the maternal and fetal blood approached a steady state at approximately 120 min. At the end of infusion these values were 1.19 ± 0.18 and 0.43 ± 0.14 ug/ml, respectively, representing an F/M ratio of 0.36. Total clearance of bupivacaine in the mother (rate of infusion/steady state plasma concentration) was 24.6 ± 3.5 ml/kg/min. In the lidocaine study, the F/M ratio at steady state was 0.55 and total maternal clearance was 55.9 ± 8.2 ml/kg/min. Maternal and fetal tissue to plasma concentration ratios of bupivacaine and lidocaine are listed in Table 2.

Table 2
Mean (± SE) Tissue to Plasma Concentration Ratios

	Bupivacaine	Lidocaine
Mother		
Brain	2.5 ± 0.4	3.4 ± 0.4
Heart	4.0 ± 1.1	3.9 ± 0.4
Lung	9.3 ± 1.7**	4.4 ± 1.1
Liver	1.2 ± 0.2	1.2 ± 0.3
Kidney	5.4 ± 0.8	6.5 ± 0.9
Adrenal	4.2 ± 0.7	5.6 ± 0.9
Fetus		
Brain	3.0 ± 0.8	4.2 ± 0.5
Heart	3.5 ± 0.8	3.3 ± 0.3
Lung	5.7 ± 1.6	6.6 ± 0.7
Liver	5.3 ± 1.7*	4.0 ± 0.3*
Kidney	4.7 ± 1.3	5.1 ± 0.6
Adrenal	5.1 ± 1.4	6.0 ± 1.0

* Significantly different from maternal liver.
** Significantly different from lidocaine.

Discussion. Compared to lidocaine, bupivacaine is cleared more slowly in the mother, presumably due to lower hepatic intrinsic extraction. The F/M ratio for bupivacaine, which was in the range reported by others in sheep (2) and humans, was significantly lower than for lidocaine. However, the F/M ratio only reflects the difference in plasma drug protein binding between mother and fetus, while, at equilibrium, plasma concentrations of free drug are similar in the mother and fetus. Maternal and fetal tissue uptake of drug (tissue/plasma concentration ratio) was generally similar for bupivacaine and lidocaine, except for the high uptake of bupivacaine in the maternal lung. These results are similar to those obtained in humans, in whom it has been shown that, although plasma protein binding is more extensive for bupivacaine than for lidocaine, the volume of distribution at steady state (based on total drug concentrations) is similar for both drugs, because tissue protein binding is also more extensive for bupivacaine (3).

References.

(1) Morishima HO, et al: Effect of lidocaine on the asphyxial responses in the mature fetal lamb. Anesthesiology 66: 502-507, 1987.
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(3) Tucker GT: Pharmacokinetics of local anaesthetics. Brit J Anaesth 58: 717-731, 1986.

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