

The Placental Transfer and Fetal Effects of Levobupivacaine, Racemic Bupivacaine, and Ropivacaine

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Background: The purposes of this study were to assess the effects of levobupivacaine on uterine blood flow and fetal well-being and to compare its placental transfer with that of bupivacaine and ropivacaine.

Methods: After a control period, pregnant ewes that were fitted with instruments for long-term monitoring were randomized to receive a two-step intravenous infusion of levobupivacaine, bupivacaine, or ropivacaine, in a blinded manner, for 1 h. Maternal and fetal hemodynamics were monitored during the study. Arterial blood samples were drawn at 30 and 60 min of infusion from the mother and fetus to determine the acid-base status (60 min only) and serum drug concentrations. The fetal brain, heart, liver, lungs, adrenal glands, and kidneys were obtained to measure tissue drug levels.

Results: Maternal blood pressure, central venous and intra-amniotic pressures, acid-base status and uterine blood flow were unaffected by any drug infusion. In contrast to the other two local anesthetics, the infusion of bupivacaine was associated with a small but significant decrease in the ewe's heart rate. At the end of the study, the heart rate in the bupivacaine-treated animals was significantly less than in the animals treated with the other two drugs. All fetuses were in good condition at the

start of study, and none of the local anesthetics affected fetal well-being. No significant differences were found among the three drugs in the maternal serum, fetal serum, fetal tissue concentrations, and tissue:serum concentration ratios.

Conclusions: Levobupivacaine was similar to bupivacaine and ropivacaine in causing no important hemodynamic changes in the pregnant ewe and fetus. There were no significant differences in the fetal serum and tissue levels of the drugs. (Key words: Local anesthetics; placental transfer; pregnancy; uterine blood flow.)

LEVOBUPIVACAINE, the single levorotary isomer of bupivacaine, is being investigated for possible use in obstetrics. It possesses the beneficial blocking properties of racemic bupivacaine (bupivacaine) but has fewer cardiotoxic effects.¹⁻³

Routine clinical use of single levorotary isomers of local anesthetics, such as ropivacaine and levobupivacaine, which produce vasoconstriction in some vascular beds,^{4,5} may reduce uteroplacental blood flow and adversely affect fetal well-being. However, ropivacaine, the first of the single-isomer local anesthetics to be introduced into clinical practice, was not found to cause uterine vasoconstriction in pregnant sheep or women undergoing cesarean delivery.^{6,7} The potential effects of levobupivacaine on uterine blood flow and the fetus are unknown.

The placental transfer of ropivacaine and levobupivacaine has not been investigated fully. Whereas studies in sheep⁶ and pregnant women⁸ have shown that these types of drugs cross the placenta readily, none has determined to what extent these local anesthetics are taken up by fetal organs. This information would be important, because the tissue, rather than the blood level, of a drug determines its physiologic effects.

The current study had two purposes. First, we wanted to compare the placental transfer and fetal tissue uptake of levobupivacaine, ropivacaine, and bupivacaine. Second, we wanted to assess the effects of levobupivacaine on uterine blood flow and fetal well-being compared with the other drugs.

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Materials and Methods

Time-dated pregnant sheep that were near term of gestation (full term, 148 days) were studied according to a protocol approved by our institutional animal care and use committee. After an overnight fast, ewes had intravascular catheters placed in the common carotid artery and jugular vein during general endotracheal anesthesia (a mixture of oxygen, nitrous oxide, and halothane). Thereafter, a laparotomy and hysterotomy were performed to fit a cannula into the fetal common carotid artery and jugular vein. During closure, a catheter was also placed in the amniotic cavity and a 4-mm "R" series pulse transit-time ultrasonic flowmeter (Transonic, Ithaca, NY), sensitive enough to detect changes in blood flow as low as 10%, was secured around a branch of the uterine artery supplying the pregnant horn.^{6,9,10} All catheters and the flowmeter cable were tunneled subcutaneously and exteriorized within a pouch attached to the ewe's flank. Thereafter, animals recovered for 4 or 5 days to allow for flow probe stabilization. The ewes were treated with antibiotics and an analgesic, flunixinmeoglumine (Banamine; Schering-Plough, Inc., NJ), for 2 days after operation.

On the day of the experiment, the ewe was weighed and kept standing in a cart. During a control period of 30–60 min and throughout the study, maternal and fetal heart rates and arterial blood pressures were recorded continuously on a polygraph. Central venous and intra-amniotic pressures and uterine blood flow also were recorded. At the conclusion of the control period, ewes were randomized to receive a two-step intravenous infusion of levobupivacaine, bupivacaine, or ropivacaine in equimolar solutions of 15.39 $\mu\text{M}/\text{ml}$. The drugs were infused *via* the maternal venous catheter at a rate of 0.014 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the first 15 min, followed by a 45-min infusion at a rate of 0.007 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. These infusion rates were chosen to achieve maternal serum concentrations of drug at 60 min, which occurred during routine epidural anesthesia for cesarean delivery (1–1.5 $\mu\text{g}/\text{ml}$).^{8,11} The investigators were blinded to the identity of the local anesthetic being infused.

Arterial blood samples were drawn from the mother and fetus during the control period and at 30 and 60 min of infusion. These time intervals were chosen, *a priori*, for two reasons. First, in a previous study, we found that the method of drug administration resulted in nearly steady state serum drug concentrations between 30 and 60 min.⁶ Second, it would be reasonable to expect the birth of the neonate within a 30- to 60-min period after

induction of epidural anesthesia using long-acting amides for cesarean delivery.¹² Nonanticoagulated samples were allowed to clot for 1 h and, after centrifugation, serum was separated and frozen until drug analysis. Anticoagulated blood samples were used to determine acid-base status and blood gas tensions at control and 60 min of infusion. Immediately after the last blood samples were taken, the fetus and then the ewe were killed with an intravenous overdose of sodium pentobarbital. The following fetal tissues were obtained and frozen until drug analysis: brain, heart, lungs, liver, adrenals, and kidneys. Drug analyses were performed using chiral normal-phase high-performance liquid chromatography with ultraviolet spectrophotometric detection. The high-performance liquid chromatography column was a 25 cm \times 4.6 mm L-phenyl glycine-based chiral column, and detection was at 210 nm. Various mobile phases based on hexane, including one or more organic modifiers, were used during this program of work. The limit of quantification for all three drugs was 50 ng/ml in serum and 100 ng/g in tissues. At least five standards were included in each calibration line, and the back-calculated concentration for each standard was within $\pm 15\%$ of the nominal concentration ($\pm 20\%$ was allowed at the limit of quantification). Replicate quality control samples, at three levels throughout the analytical range, were prepared and analyzed along with each analytical batch. The quality control samples were prepared on the day of analysis in the appropriate control matrix, and the back-calculated concentration for the quality control samples was required to be within $\pm 15\%$ of the nominal concentration for the batch to be accepted.

Analyses of variance were performed to evaluate differences between and across drug treatment groups. Weight and gestational age were used as variables to determine that no obvious signs of bias were introduced by the randomization process. Absolute changes from baseline were calculated at 30 and 60 min, where appropriate, for each variable, and a Bartlett test was performed to check the assumption of equal variances between drug groups. When this test was significant, the data were ranked and analysis of variance was performed with a Shapiro-Wilk test for the assumption of normality. Significant differences within drug treatment groups were identified using the Scheffé test for multiple comparisons. All results are expressed as the mean \pm SD. $P < 0.05$ was considered significant. We estimated that 10 sheep would be necessary in each group to detect a 25% change from control in uterine blood flow, with a β error of 0.8 and an α error of 0.05.^{6,10}

Table 1. Weight and Gestational Age on the Day of Study and Total Drug Administered during the Study

	Levobupivacaine (n = 10)	Bupivacaine (n = 10)	Ropivacaine (n = 10)
Weight (kg)	64 ± 10	60 ± 11	60 ± 7
Gestational age (days)	134 ± 3	133 ± 3	134 ± 3
Total infused (ml/kg)	0.53 ± 0.01	0.53 ± 0.01	0.53 ± 0.01
Total drug (μm/kg)	8.08 ± 0.19	8.08 ± 0.08	8.11 ± 0.19

Differences are not statistically different.

Results

Ten ewes of comparable maternal weight and gestational age were studied in each group (table 1). All ewes were in good condition, and there were no significant differences in heart rate, mean arterial blood pressure, pH, and gas tensions among the drug groups at the start of the study. The total amount of drug administered during the study was similar for the three groups (table 1). Infusion of bupivacaine was associated with a small but significant decrease in heart rate from 104 ± 23 beats/min at control to 82 ± 15 beats/min at 60 min of infusion (table 2) ($P < 0.05$). The heart rate at the end of

Table 2. Maternal Heart Rate (HR), Mean Arterial Blood Pressure (MABP), Uterine Blood Flow (UBF), Intraamniotic Pressure (IA), and Central Venous Pressure (CVP) before (0) and at 30 and 60 min of Infusion

	0 min	30 min	60 min
Levobupivacaine			
HR (beats/min)*	95 ± 10	94 ± 15	87 ± 10
MABP (mmHg)*	88 ± 5	89 ± 4	88 ± 6
UBF (ml/min)	457 ± 139	453 ± 127	450 ± 136
IA (mmHg)	5 ± 4	5 ± 4	5 ± 3
CVP (mmHg)*	6 ± 4	7 ± 4	7 ± 4
Bupivacaine			
HR (beats/min)	104 ± 23	89 ± 20	82 ± 15†‡
MABP (mmHg)	89 ± 10	90 ± 11	89 ± 10
UBF (ml/min)	466 ± 121	472 ± 113	469 ± 127
IA (mmHg)	7 ± 3	7 ± 3	7 ± 3
CVP (mmHg)	6 ± 1	7 ± 1	7 ± 4
Ropivacaine			
HR (beats/min)	108 ± 20	101 ± 19	102 ± 18
MABP (mmHg)	91 ± 12	90 ± 10	89 ± 13
UBF (ml/min)	451 ± 118	453 ± 119	467 ± 119
IA (mmHg)	6 ± 3	4 ± 3	5 ± 3
CVP (mmHg)	4 ± 4	5 ± 5	6 ± 5

* Due to technical difficulties, n = 9 measurements.

† Significantly different from control (0 min) ($P < 0.05$).

‡ Significantly different from other drug groups ($P < 0.05$).

Table 3. Fetal Heart Rate (HR) and Mean Arterial Blood Pressure (MABP) before and at 30 and 60 min of Infusion and Arterial Blood pH and Gas Tensions before and at the End of Infusion

	0 min	30 min	60 min
Levobupivacaine			
HR	155 ± 13	153 ± 11	151 ± 7
MABP	45 ± 6	48 ± 6	47 ± 5
pH	7.40 ± 0.02		7.39 ± 0.04
P _{CO2}	45 ± 5		44 ± 4
P _{O2}	20 ± 4		25 ± 6
Bupivacaine			
HR	153 ± 14	151 ± 16	150 ± 16
MABP	46 ± 5	49 ± 5	49 ± 4
pH*	7.41 ± 0.02		7.41 ± 0.02
P _{CO2} *	45 ± 2		44 ± 3
P _{O2} *	20 ± 3		21 ± 4
Ropivacaine			
HR	164 ± 14	159 ± 14	159 ± 16
MABP	44 ± 7	47 ± 7	47 ± 6
pH	7.40 ± 0.03		7.40 ± 0.02
P _{CO2}	43 ± 4		43 ± 3
P _{O2}	22 ± 5		22 ± 5

Differences within and among drug groups are not statistically significant.

* Due to technical difficulties, n = 9 measurements.

the study was significantly less for bupivacaine-treated ewes compared with the animals in the levobupivacaine and ropivacaine groups (table 2; $P = 0.003$). There were no significant changes from baseline in blood pressure, uterine blood flow, and intraamniotic and central venous pressures at 30 and 60 min of infusion with any of the local anesthetics (table 2). The acid-base state and blood gas tensions also were unaffected.

All fetuses were healthy at the start of the study, and maternal infusion of levobupivacaine, bupivacaine, or ropivacaine did not significantly change the parameters of well-being, such as heart rate, mean arterial blood pressure, pH, and gas tensions (table 3).

There were no significant differences among the three drugs in the maternal serum concentrations achieved at 30 and 60 min of infusion (fig. 1). The corresponding mean serum concentrations were considerably less in the fetus than in the ewe. There were no significant differences in fetal serum concentrations among the three local anesthetics (fig. 1). Figure 2 shows the fetal tissue drug concentrations. Generally, tissue levels of all three drugs were greater than the corresponding fetal serum concentrations. There were also no significant differences in individual tissue drug concentrations or tissue:serum concentration ratios of levobupivacaine, bupivacaine, and ropivacaine (figs. 2 and 3).

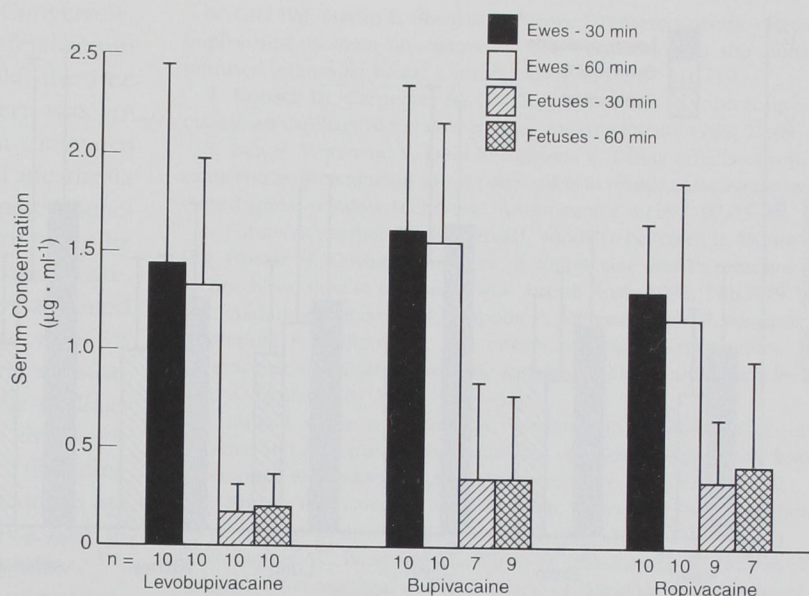


Fig. 1. Serum concentrations ($\mu\text{g}/\text{ml}$) of levobupivacaine, bupivacaine, and ropivacaine in ewes and fetuses at 30 and 60 min of infusion. (Because of technical problems, fetal serum drug concentrations could not be determined in every study.)

Discussion

These data indicate that maternal intravenous infusion of levobupivacaine, bupivacaine, and ropivacaine produced no important changes in the pregnant ewe or her fetus. In the ewe, infusion of all three local anesthetics resulted in steady state serum concentrations at 30 and 60 min within the range of those observed during epidural anesthesia for cesarean section. For instance, in recent studies, the mean peak maternal serum concentrations of levobupivacaine, ropivacaine, and bupivacaine were 1, 1.3, and 1.1 $\mu\text{g}/\text{ml}$, respectively, after epidural administration for cesarean de-

livery.^{8,11} In contrast to levobupivacaine and ropivacaine, infusion of bupivacaine was associated with a small but significant decrease in maternal heart rate that was not physiologically important to the ewe. This could have been related to depressant effects on the myocardium and conduction system, which are greater with bupivacaine than with the other drugs.^{3,13,14} Mean arterial blood pressure, pH, and gas tensions were not affected by any of the drugs infused.

The Doppler flow probe used in this study can detect relatively small changes in uterine blood flow.^{6,9,10} The

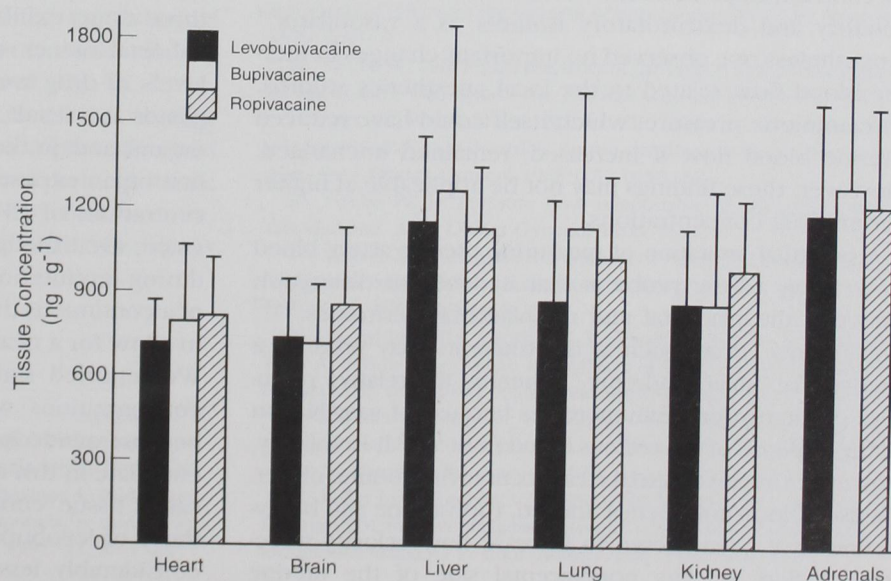


Fig. 2. Fetal tissue concentrations (ng/g) of levobupivacaine, bupivacaine, and ropivacaine at 60 min of infusion.

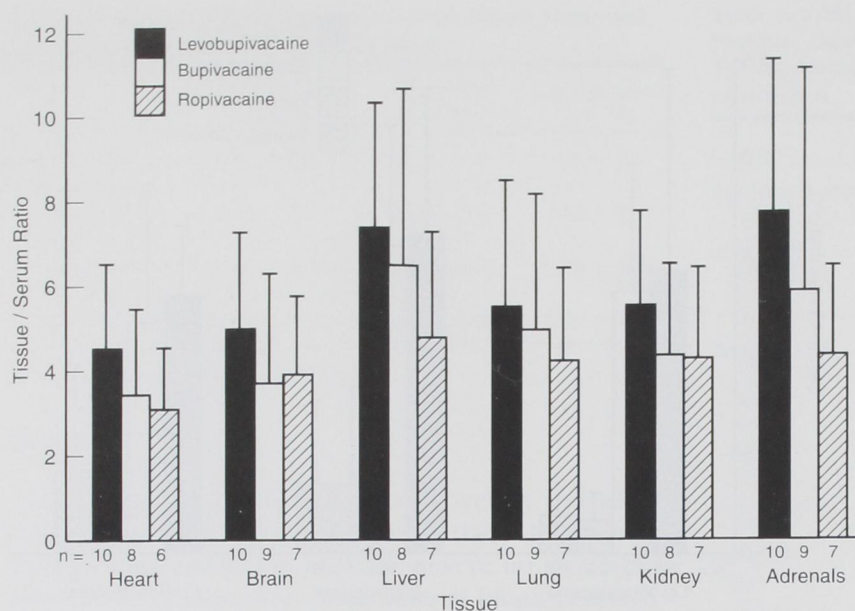


Fig. 3. Fetal tissue:serum concentration ratios of levobupivacaine, bupivacaine, and ropivacaine at 60 min of infusion.

appropriateness of using this model to study decreases in uterine blood flow was established in our previous studies in which infusions of dopamine or epinephrine to the ewe resulted in 20–25% decreases in uterine blood flow, whereas saline infusion did not.^{6,10} Control values (and standard deviations) for uterine blood flow in the current study are in good agreement with the results of our previously published work.⁶

In routine clinical use, ropivacaine and levobupivacaine would be expected to cause vasoconstriction because they are single levorotary isomer formulations.^{4,15} In contrast, bupivacaine, a racemic mixture of the levorotary and dextrorotary isomers, is a vasodilator.⁴ Nonetheless, we observed no important changes in uterine blood flow related to the local anesthetics studied. Intraamniotic pressure, which itself could have reduced uterine blood flow if increased, remained unchanged. However, these findings may not be applicable at higher serum drug concentrations.

A potential limitation of measuring uterine artery blood flow using a flow probe is that it does not distinguish between the placental and nonplacental perfusions.^{16,17} For instance, drugs such as isoproterenol may produce a myometrial "steal syndrome," whereby the relative perfusion of the myometrium increases because of vasodilation at the expense of intervillous blood flow.^{17,18} It is unlikely, however, that myometrial steal occurs with routine obstetric use of local anesthetics. Indeed, ropivacaine and bupivacaine have been shown to increase flow velocity waveform indices on the nonplacental side of the uterine

circulation, suggesting that resistance to flow in the myometrium is increased.⁷ The fact that parameters of fetal well-being, such as heart rate, arterial pH, and gas tensions, were unaffected in our study further supports the assumption that placental circulation was maintained during local anesthetic infusions.

The fetal serum concentrations of drug were similar for all three local anesthetics and were not associated with any important hemodynamic changes in the non-asphyxiated mature fetal lamb. To our knowledge, this is the first time that fetal tissue concentrations of ropivacaine and levobupivacaine have been measured. All three drugs exhibited similar concentrations in individual fetal tissues studied. It is not surprising that high levels of drug were found in the liver and the adrenal glands as a result, in part, of the high perfusion of these organs, and, in the case of the liver, of its location as the first organ exposed to umbilical vein blood.¹⁹ Lung concentrations of all three local anesthetics also were elevated, even though the lung is a poorly perfused organ during intrauterine life. This could be related to the use of a continuous drug infusion over a period long enough to allow for a nearly steady state to develop in the fetus. We reported similar findings with lidocaine.²⁰ Tissue concentrations were not determined in the placenta because amide local anesthetics do not significantly accumulate in this organ.²¹ It was unexpected that ropivacaine tissue concentrations would be comparable to those of levobupivacaine and bupivacaine because it is considerably less lipid soluble (n-heptane:buffer parti-

tion coefficient) than the other two drugs.²² Conversely, ropivacaine exhibits less binding to adult and fetal serum proteins than does bupivacaine. For example, the free fraction of ropivacaine at the time of delivery was approximately twice that of bupivacaine in neonates whose mothers received the drug for epidural anesthesia during cesarean section.⁸ Perhaps any anticipated benefits to be gained from lower lipid solubility are offset by a greater availability of free ropivacaine for tissue uptake.

Based on the results of published studies, we assumed that 0.5% levobupivacaine was equieffective to 0.5% bupivacaine and 0.5% ropivacaine for epidural anesthesia during cesarean delivery.^{8,11} However, our findings may not be applicable to the use of these drugs for epidural analgesia during labor. For instance, the minimum local analgesic concentration of ropivacaine is approximately 50% greater than that for bupivacaine in women undergoing epidural analgesia during labor.²³

In the current study, a sufficient number of animals were studied to detect a 25% difference in the means with 80% power. We may have missed a significant difference, albeit less than 25%, among the means of physiologic variables and fetal tissue concentrations. However, these differences were less than 15% and probably of no biologic or pharmacologic significance. In contrast, the differences between the mean fetal serum concentration of levobupivacaine, 0.2 µg/ml, and those of bupivacaine and ropivacaine, 0.35 and 0.42 µg/ml, respectively, were greater than 25% but were not significant because of low *post hoc* power (<50%). This may be the result of greater interindividual variation in fetal serum concentrations in the bupivacaine and ropivacaine groups and also of the fact that, for technical reasons, the fetal serum concentration could not be determined reliably in every experiment (fig. 1).

In conclusion, during the conditions of the current study, levobupivacaine was similar to ropivacaine and bupivacaine in producing no important hemodynamic changes in the pregnant ewe and her fetus. Furthermore, the fetal serum levels and tissue uptake of all three drugs were similar.

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