

Systemic Toxicity of Ropivacaine during Ovine Pregnancy

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Ropivacaine is a new amide local anesthetic structurally related to bupivacaine and mepivacaine. Its potency and duration of action are similar to those of bupivacaine but its therapeutic index may be greater. Since pregnancy enhances the cardiotoxicity of bupivacaine, the current study was devised to compare the toxicity of ropivacaine in chronically instrumented nonpregnant and pregnant ewes during continuous intravenous infusion of the drug at the rate of $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. In all animals, symptoms of local anesthetic toxicity occurred in the usual order—convulsions, hypotension, apnea, and circulatory collapse. There were no significant differences between the two groups of animals in the doses and plasma concentrations of ropivacaine associated with each toxic manifestation. For example, circulatory collapse occurred at a mean dose of $11.3 \pm 1.1 \text{ mg} \cdot \text{kg}^{-1}$ in nonpregnant and $12.4 \pm 0.9 \text{ mg} \cdot \text{kg}^{-1}$ in pregnant animals, with corresponding plasma concentrations of 7.3 ± 0.3 and $9.6 \pm 2.1 \mu\text{g} \cdot \text{ml}^{-1}$ ($P = \text{not significant}$). Protein binding of ropivacaine in the concentration range associated with toxic manifestations was similar in sera obtained from nonpregnant and pregnant ewes. In conclusion, ovine pregnancy does not enhance the systemic toxicity of ropivacaine, possibly because of an absence of gestation-related increase in the availability of free drug. (Key words: Anesthesia: obstetrics. Anesthetics, local: ropivacaine; toxicity. Protein binding: ropivacaine.)

BUPIVACAINE has been found to have a margin of safety narrower than that of less potent agents such as lidocaine and mepivacaine.¹⁻⁴ In several patients, unintended intravenous injection of bupivacaine has resulted in cardiovascular collapse, in some cases refractory to resuscita-

tion.^{5,6} Some of these mishaps occurred in parturients during attempted induction of epidural anesthesia.

Ovine pregnancy has been shown to enhance the cardiotoxicity of bupivacaine³ but not of mepivacaine⁴ or lidocaine.⁷ In the cases of bupivacaine and mepivacaine, this difference has been shown to be related in part to gestational increases in the availability of unbound bupivacaine.⁴

Ropivacaine is a new amide local anesthetic that is structurally related to bupivacaine and mepivacaine. Its potency and duration of action are similar to those of bupivacaine, but its cardiotoxicity may be less.⁸⁻¹² With bupivacaine it has been shown that the dose and plasma concentration necessary to produce circulatory collapse were significantly less in pregnant than in nonpregnant ewes.³ The current study was undertaken to determine whether the systemic toxicity of ropivacaine also is affected by pregnancy.

Materials and Methods

Seven nonpregnant and five pregnant ewes were studied under a protocol approved by the Institutional Animal Care and Use Committee. The same animals had been studied 4-5 days earlier to determine the effects of pregnancy on ropivacaine disposition.¹³

The details of surgical preparation have been described previously.¹³ Briefly, after an overnight fast, spinal anesthesia was induced with 10-12 mg of tetracaine hydrochloride, and polyethylene catheters were inserted into the femoral vessels of nonpregnant and pregnant ewes. Surgical preparation of the fetus was pertinent only to the aforementioned study¹³ of the pharmacokinetics of ropivacaine. Mothers and fetuses were given antibiotics throughout the recovery and study periods.

On the day of the study (7-9 days after surgery), the ewe was placed in a cart, free to stand or lie down, and electrocardiographic electrodes were attached to her extremities for intermittent ECG recording. Heart rate (cardiotachometer) and arterial blood pressure were monitored, and recorded continuously on a polygraph. Ropivacaine hydrochloride 0.5% (Astra[®]) was infused into the femoral vein of all animals at a constant rate of $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ until circulatory collapse. Arterial blood samples were obtained at the onset of each toxic manifestation, which occurred in the sequence previously described^{3,4,7}—convulsions, hypotension, apnea, and circulatory collapse. Hypotension was defined as occurring with a precipitous drop in the arterial blood pressure,

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which had been elevated from the onset of convulsions. Apnea was diagnosed after no respirations were noted for at least 20 s. Circulatory collapse was defined as the absence of blood pressure. After determination of blood pH and gas tensions, samples were centrifuged, and plasma separated and frozen. After circulatory collapse, the brain and heart were removed and weighed and were frozen until drug analysis.

Thereafter, plasma and tissue concentrations of ropivacaine were determined by a gas chromatographic technique similar to that previously described by Tucker.¹⁴ The sensitivity of this assay was $0.05 \mu\text{g} \cdot \text{ml}^{-1}$; the coefficient of variation ranged from 5% at $0.10 \mu\text{g} \cdot \text{ml}^{-1}$ to 2% at $1.00 \mu\text{g} \cdot \text{ml}^{-1}$ during the course of this study.

The mean doses and plasma concentrations of ropivacaine associated with each toxic manifestation as well as the mean tissue drug concentrations at circulatory collapse were compared in nonpregnant and pregnant animals using Student's *t* test for unpaired data. Since repeated statistical testing was performed for ropivacaine doses and plasma concentrations, Bonferroni's correction factor, increasing the threshold for significance to $P < 0.0125$, was applied. Analyses of variance for repeated measures with Sheffé's *F* test were used to evaluate differences from preinfusion values (control) for heart rate, blood pressure, pH, and gas tensions at the onset of each toxic manifestation, with $P < 0.05$ considered statistically significant. All results are reported as the mean \pm standard error of the mean.

In order to determine serum protein binding of ropivacaine, an additional four nonpregnant and five pregnant ewes near term, unexposed to any drugs, were obtained from our regular supplier. Blood was drawn by venipuncture and was allowed to clot for approximately 30 min. Contact with polystyrene plastic or stoppers containing tributoxyethyl phosphate ester (TBEP) plasticizer was avoided. After centrifugation, the serum samples were frozen at -20°C until required for study. Serum, rather than plasma, was chosen in order to avoid the artifactual effects of *in vitro* lipolysis, which is particularly significant in the plasma of pregnant animals.^{15,16}

Studies were conducted within 1 week of blood collection. Serum pH was first adjusted with hydrochloric acid or sodium hydroxide to be 7.50 ± 0.02 , which is physi-

ologic for the ovine species. Ropivacaine was added to 5-ml aliquots of serum to achieve a range of drug concentrations including those found to be associated with toxicity. The serum and drug were allowed to equilibrate for at least 1 h at room temperature. Using an ultrafiltration system (Amicon[®] MPS-1 with YMT membranes), serum water was obtained from 1-ml aliquots of serum. With one exception, two replicate samples were tested at each concentration. Centrifugation was for 45 min at $2,000 \times g$. Thereafter, drug concentrations in serum and serum water were determined as already stated.¹⁴ Previous studies have shown that equilibrium dialysis of serum and this ultrafiltration technique produce comparable results, and that there is no binding of local anesthetics to the membrane.¹⁷ The unpaired Student's *t* test was used to detect differences between protein binding of drugs in sera from pregnant and nonpregnant animals. Bonferroni's correction factor for repeated testing was applied, with a *P* value of less than 0.0125 considered significant.

Results

Pregnant ewes ($n = 5$) were studied near term of gestation, 136.6 ± 0.8 days. Their weight, 65.0 ± 2.6 kg, was greater than that of nonpregnant ewes ($n = 7$), 56.6 ± 4.1 kg. All animals were in good condition prior to study; mean heart rate, arterial blood pressure, pH, and blood gas tensions were within the normal range for our laboratory (tables 1 and 2).

The signs of systemic toxicity occurred in the same sequence as previously described for other amide local anesthetics: convulsions were followed by hypotension, apnea, and, finally, circulatory collapse.^{3,4,7} Seizure activity started at similar drug doses in nonpregnant and pregnant ewes, $6.1 \pm 0.6 \text{ mg} \cdot \text{kg}^{-1}$ and $5.9 \pm 0.6 \text{ mg} \cdot \text{kg}^{-1}$, respectively ($P = 0.80$) (fig. 1). The corresponding ropivacaine plasma concentrations also were similar, namely $4.3 \pm 0.5 \mu\text{g} \cdot \text{ml}^{-1}$ in nonpregnant and $5 \pm 0.7 \mu\text{g} \cdot \text{ml}^{-1}$ in pregnant ewes ($P = 0.44$) (fig. 2). With the onset of convulsions, mean heart rate increased significantly, from a control value of 97 ± 4 to 193 ± 13 beats per min in nonpregnant and from 106 ± 19 to 166 ± 24 beats per min in pregnant sheep, while the mean arterial blood pressure approximately doubled in both groups of animals (table 1).

TABLE 1. Heart Rate and Mean Arterial Pressure at the Onset of Each Toxic Manifestation during Ropivacaine Infusion

	Control	Convulsions	Hypotension	Apnea
Nonpregnant				
HR (beats per min)	97 ± 4	$193 \pm 13^*$	$181 \pm 14^*$	$147 \pm 19^*$
MAP (mmHg)	106 ± 6	$220 \pm 7^*$	$100 \pm 11^\dagger$	$66 \pm 12^*$
Pregnant				
HR (beats per min)	106 ± 19	$166 \pm 24^*$	$143 \pm 17^*$	$150 \pm 12^*$
MAP (mmHg)	94 ± 8	$187 \pm 22^*$	$91 \pm 16^\dagger$	$29 \pm 7^*$

Mean \pm SE.

HR = heart rate; MAP = mean arterial pressure.

* Significantly different from control.

† Significantly different from convulsions.

TABLE 2. Arterial Blood Gas Data at Each Toxic Manifestation during Ropivacaine Infusion

	Control	Convulsions	Hypotension	Apnea	Circulatory Collapse
Nonpregnant					
pH	7.52 ± 0.01	7.53 ± 0.02	7.24 ± 0.03*	7.22 ± 0.03*	7.20 ± 0.03*
P _a CO ₂ (mmHg)	33 ± 0.5	29 ± 1	54 ± 3*	55 ± 3*	58 ± 3*
P _a O ₂ (mmHg)	83 ± 4	81 ± 5	32 ± 4*	25 ± 3*	21 ± 2*
Pregnant					
pH	7.53 ± 0.02	7.55 ± 0.02	7.31 ± 0.02*	7.29 ± 0.03*	7.25 ± 0.01*
P _a CO ₂ (mmHg)	30 ± 1	28 ± 1	47 ± 4*	45 ± 4*	51 ± 3*
P _a O ₂ (mmHg)	83 ± 3	81 ± 6	39 ± 8*	32 ± 9*	21 ± 1*

Mean ± SE.

* Significantly different from control.

Arterial blood pH and gas tensions were unchanged at the onset of convulsions in both groups of animals (table 2). In nonpregnant as well as in pregnant ewes, by the time hypotension occurred, pH and arterial oxygen tension had decreased, whereas arterial carbon dioxide tension had increased. Drug doses required to induce hypotension were similar in both groups, 10.5 ± 1.1 mg · kg⁻¹ in nonpregnant and 11.7 ± 0.9 mg · kg⁻¹ in pregnant ewes (*P* = 0.45) (fig. 1), as were plasma concentrations, 5.8 ± 0.6 μg · ml⁻¹ and 6.9 ± 0.3 μg · ml⁻¹ (*P* = 0.19) (fig. 2).

Circulatory collapse occurred within 1 min of apnea in both groups, at a mean dose of 11.3 ± 1.1 mg · kg⁻¹ in nonpregnant and 12.4 ± 0.9 mg · kg⁻¹ in pregnant ewes (*P* = 0.48) (fig. 1), with corresponding plasma concentrations of 7.3 ± 0.3 and 9.6 ± 2.1 μg · ml⁻¹ (*P* = 0.23) (fig. 2). The ratios of dosages and plasma concentrations resulting in circulatory collapse and those required for convulsions (CC/CNS) also were not different between nonpregnant and pregnant animals (table 3). A brief episode of ventricular tachycardia occurred in each of two nonpregnant animals and was the terminal event in one pregnant ewe.

Mean brain concentrations of ropivacaine measured after circulatory collapse were similar in nonpregnant and pregnant ewes, at 31.3 ± 2.9 and 35.0 ± 0.7 μg · g⁻¹, respectively (*P* = 0.25), as were drug concentrations in the heart, at 26.7 ± 2.8 (nonpregnant) and 30.5 ± 1.2 μg · g⁻¹ (pregnant) (*P* = 0.14).

Protein binding studies were performed on sera obtained from four nonpregnant and five pregnant ewes. The mean ropivacaine serum concentrations tested were similar between the two groups, ranging from 1.7 ± 0.1 to 8.6 ± 0.2 μg · ml⁻¹ in the nonpregnant and 1.7 ± 0.2 to 9.1 ± 0.1 μg · ml⁻¹ in the pregnant animals (table 4). The percentage of ropivacaine bound to serum proteins in nonpregnant ewes was 65 ± 4% at the lowest concentration tested and 48 ± 3% at the highest, compared to 64 ± 9 and 51 ± 5% at equivalent serum concentrations from pregnant ewes.

Discussion

The doses and plasma concentrations of ropivacaine required to produce toxic manifestations were not different between the two groups of animals, indicating that gestation does not alter the systemic toxicity of ropiva-

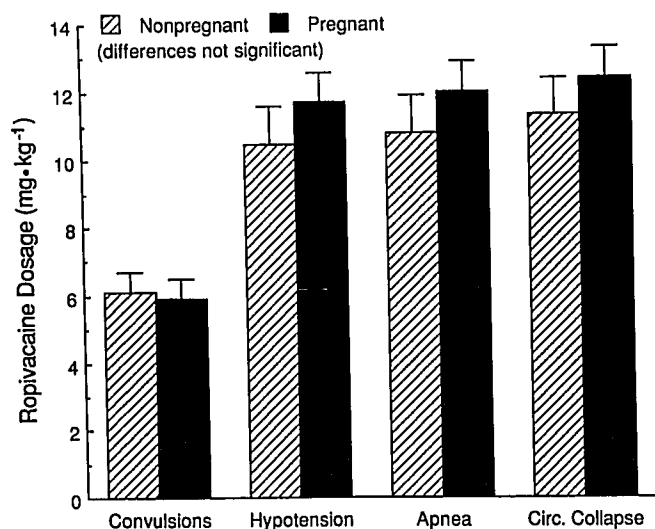


FIG. 1. Mean (±SE) dosages of ropivacaine administered to nonpregnant and pregnant ewes up to the onset of each toxic manifestation.

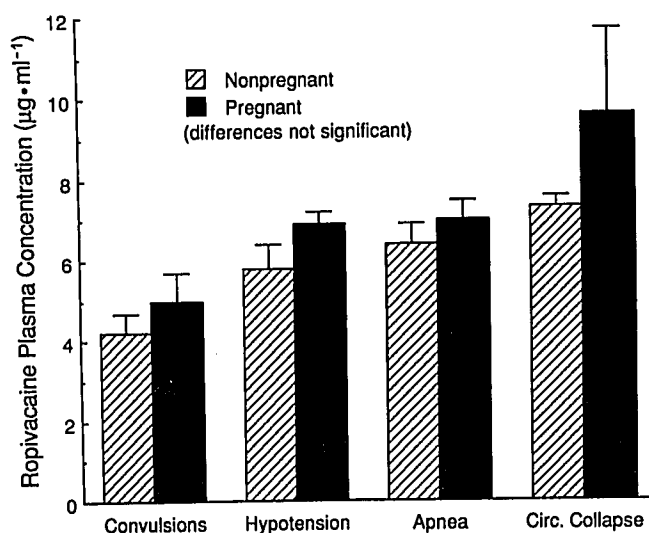


FIG. 2. Mean (±SE) plasma concentrations of ropivacaine at each toxic manifestation in nonpregnant and pregnant ewes.

TABLE 3. Ratios of Circulatory Collapse and Convulsive Ropivacaine Dosages and Plasma Concentration at Onset of Each Toxic Manifestation

	Nonpregnant	Pregnant
Dosage	1.9 ± 0.1	2.2 ± 0.3
Plasma concentration	1.8 ± 0.1	2.0 ± 0.05

Mean ± SE.

Differences between groups not significant.

caine. In this regard, ropivacaine appears to be similar to mepivacaine and lidocaine^{4,7} but different from bupivacaine, which has produced fatal toxic manifestations at lower doses and plasma concentrations in pregnant compared to nonpregnant ewes.³ The difference between mepivacaine and bupivacaine was attributed to the fact that the proportion of mepivacaine bound to serum proteins at drug concentrations associated with circulatory collapse was similar in nonpregnant and pregnant sheep, whereas pregnancy was associated with significant reductions in bupivacaine serum protein binding.⁴

Protein binding of ropivacaine in this study was measured with a similar protocol and under conditions similar to those used to measure protein binding of bupivacaine and mepivacaine in an earlier study.⁴ However, in this study, ewes were obtained from a different supplier, and blood was drawn from individual animals without pooling. Nonetheless, the protein binding data obtained indicate that, at concentrations associated with circulatory collapse, ovine pregnancy is not associated with increased availability of free ropivacaine.

The concentration of ropivacaine in myocardium obtained from both pregnant and nonpregnant animals was similar. In prior reports, pregnancy did not alter myocardial uptake of mepivacaine or bupivacaine.^{3,4} Ropivacaine concentrations in the brain also were similar in nonpregnant and pregnant ewes, in contrast to data for mepivacaine and bupivacaine showing that brain concentrations of mepivacaine were higher and those of bupivacaine lower during pregnancy. The reason for these differences is not clear, and neither is their significance, since brain concentrations of local anesthetics were not determined at the onset of convulsions.

TABLE 5. Dosage and Plasma Concentration of Ropivacaine and Bupivacaine at Onset of Convulsions and Circulatory Collapse

	Ropivacaine	Bupivacaine*
Nonpregnant		
Dosage (mg · kg ⁻¹)		
Convulsions	6.1 ± 0.6†	2.7 ± 0.4
Circulatory collapse	11.3 ± 1.1	8.9 ± 0.9
Plasma concentration (μg · ml ⁻¹)		
Convulsions	4.2 ± 0.5	5.2 ± 0.9
Circulatory collapse	7.3 ± 0.3	8.0 ± 0.9
Pregnant		
Dosage (mg · kg ⁻¹)		
Convulsions	5.9 ± 0.6†	1.9 ± 0.6
Circulatory collapse	12.4 ± 0.9†	5.1 ± 0.1
Plasma concentration (μg · ml ⁻¹)		
Convulsions	5.0 ± 0.7	4.2 ± 0.4
Circulatory collapse	9.6 ± 2.1	5.5 ± 0.8

† Significantly different from bupivacaine (unpaired Student's *t* test).* Previously published data.³

In the current study, malignant ventricular arrhythmias, commonly occurring during bupivacaine intoxication,³ were rare. This is similar to the finding in dogs, in which ropivacaine was associated with a lower incidence of ventricular arrhythmias than was bupivacaine.⁹ Administration of ropivacaine to pigs did not result in ventricular arrhythmias.¹⁰ *In vitro*, ropivacaine has been shown to be less potent than bupivacaine in terms of its depressant effect on cardiac excitation and conduction, and thus it is less likely to produce ventricular arrhythmias of a reentrant type.¹²

In table 5, doses and plasma concentrations of ropivacaine are compared to those of bupivacaine obtained from a previous study.³ Since they are approximately equipotent, the two drugs were infused at the same rate, 0.5 mg · kg⁻¹ · min⁻¹. In both nonpregnant and pregnant ewes, the doses of ropivacaine required to produce convulsions were greater than those of bupivacaine. Similarly, early signs of central nervous system (CNS) toxicity in male volunteers occurred at doses of ropivacaine that were significantly greater than those of bupivacaine.¹⁸ In male dogs there was no significant difference between the doses of ropivacaine and bupivacaine required to cause sei-

TABLE 4. Percentage of Ropivacaine Bound to Serum Proteins at Different Serum Concentrations

Serum Concentration (μg · ml ⁻¹)		<i>P</i>	Protein Bound (%)		<i>P</i>
Nonpregnant (n = 4)	Pregnant (n = 5)		Nonpregnant (n = 4)	Pregnant (n = 5)	
1.7 ± 0.1	1.7 ± 0.2	0.98	65 ± 4	64 ± 9	0.91
3.8 ± 0.1	4.0 ± 0.1	0.16	57 ± 5	54 ± 7	0.74
6.4 ± 0.2	6.8 ± 0.1	0.16	52 ± 2	54 ± 6	0.78
8.6 ± 0.2	9.1 ± 0.1	0.052	48 ± 3	51 ± 5	0.58

Mean ± SE.

Differences not significant.

zures,⁹ but a drug infusion rate four times greater than that used in the current study was used. However, bolus injection of two times the convulsive dose of either drug in these dogs resulted in a greater incidence of death in the bupivacaine-treated animals. Recent clinical studies comparing the anesthetic efficacy of ropivacaine and bupivacaine indicate that the two agents are similar in terms of onset, anesthetic potency, and duration of action after epidural and brachial plexus blockade.^{19,20} Thus, currently available data suggest that ropivacaine possesses a greater margin of safety than bupivacaine.

While there was no difference between nonpregnant and pregnant ewes in the dose of ropivacaine necessary to produce circulatory collapse, a significantly smaller dose of bupivacaine was required in pregnant compared to nonpregnant animals.³ The doses of bupivacaine were less than those reported here for ropivacaine, but only in pregnant ewes did the difference between the two drugs reach statistical significance.

The plasma concentrations associated with convulsions and circulatory collapse in nonpregnant and pregnant ewes were similar for both drugs. This may be due to pharmacokinetic differences between them, since values for the clearance of ropivacaine are greater than those for bupivacaine in both dogs and humans.^{21,22}

In conclusion, pregnancy does not seem to enhance ropivacaine toxicity in sheep. Further, doses required to produce signs of CNS and cardiac toxicity in pregnant ewes are greater for ropivacaine than for bupivacaine. Extrapolation of the results of this study to the clinical situation of unintended intravascular injection may be restricted by our choice of methodology. Whereas in sheep circulatory collapse occurred only after 20–25 min of infusion, in humans, a bolus injection of bupivacaine may result in immediate cardiac arrest. The slower rate of administration allows more extensive redistribution of drug to less well-perfused organs. Consequently, with a bolus injection, toxic manifestations occur at lower doses but higher drug concentrations in the blood.²³ Nonetheless, since comparisons between nonpregnant and pregnant ewes were made under similar experimental conditions, the results suggest that ropivacaine may be a safer drug than bupivacaine for use in obstetric anesthesia.

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