THE DIRECT EFFECTS OF CIRCULATING LIDOCAINE ON UTERINE BLOOD FLOW AND FOETAL WELL-BEING IN THE PREGNANT EWE

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HUMAN OR OVINE UTERINE VESSELS constrict when exposed *in vivo* or *in vitro* to high concentrations of local anaesthetics.¹⁻³ Uterine tone also increases.³ Griess, *et al.* achieved a uterine arterial lidocaine concentration of 40 $\mu\text{gm/ml}$ by injecting lidocaine into the aorta of non-pregnant ewes, causing a 25 per cent reduction in uterine blood flow. This toxic blood level far exceeds the usual levels of 2 to 4 $\mu\text{gm/ml}$ normally obtained during epidural blocks for labour and delivery.⁴⁻¹⁰ Systemic levels greater than 5 to 10 $\mu\text{gm/ml}$ produce toxicity.¹¹ However, because of the importance of uterine blood flow to foetal well-being, we have studied whether lidocaine levels in the usual clinical range reduced uterine blood flow or had adverse effects on maternal and foetal cardiovascular status in the pregnant ewe.

METHOD

We studied 13 pregnant ewes near term (mean gestational age 132 days; range 130-135 days). Each ewe carried a single foetus. All animals underwent preparatory surgery while anaesthetized with halothane in oxygen. Polyvinyl catheters (#8 French, 0.105" OD) were placed through groin incisions into both maternal femoral arteries and veins, and through the external jugular vein into the right atrium. One arterial catheter was used for continuous recording of maternal blood pressure and pulse rate, while the other was used for arterial blood sampling and, together with the right atrial catheter, for measurement of cardiac output by the cardiogreen dye-dilution technique. Through a mid-line abdominal incision a precalibrated Statham electromagnetic Flo-Probe® was secured to a branch of the uterine artery supplying the pregnant horn. Through a small hysterotomy incision a polyvinyl catheter (#4 French, 0.053" OD) was inserted into a foetal femoral artery for arterial sampling and measurement of blood pressure and heart rate. An additional polyvinyl catheter (#8 French, 0.105" OD) was placed in the amniotic fluid cavity for pressure measurements. The uterus was closed and the suture line oversewn to prevent leakage of amniotic fluid.

At least 24 hours elapsed between the above preparations and the conduct of a study. Throughout each experiment, maternal and foetal blood pressures and

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pulse rates were recorded continuously using Statham P23 D1 strain gauges connected to a Grass polygraph. Uterine blood flow was measured continuously using a Statham SP 2022 blood flowmeter with a non-occlusive zero.

Maternal and foetal arterial blood samples were obtained at 15-minute intervals and analyzed immediately after sampling with an Instrumentation Laboratories 313 Blood Gas Analyzer. The results were corrected for temperature measured by a Yellow Springs rectal probe. Maternal and foetal base excess values were calculated using the Severinghaus slide rule.¹² Cardiac outputs were measured at 15-minute intervals with a Waters Densitometer.

Each study was divided into two periods. The first was a 30-minute control period with the ewe standing quietly in her cage. The 30-minute period was defined by stable maternal and foetal cardiovascular and acid-base values. Control values for blood pressure, pulse rate, and uterine blood flow were means of determinations made at five-minute intervals during this period, while control values for cardiac output, stroke volume, total peripheral resistance and acid-base data were means of determinations taken at 15-minute intervals (Tables I and II).

During the second period (2 hours and 15 minutes) lidocaine was infused into the maternal femoral vein first at a rate of 0.25 mg/kg/min for 15 minutes (priming dose) and then at a rate of 0.15 mg/kg/min for two hours.¹³ Arterial blood was drawn at 15-minute intervals from both mother and foetus for measurement of lidocaine concentration using a gas chromatographic method.¹⁴

All cardiovascular values during the lidocaine infusion period are given as per cent change from control. Values for blood pressure, pulse rate and uterine blood flow in each 15-minute interval (Table I) represent the means of three consecutive determinations made at five-minute intervals. Analysis of variance, one way classification, was used to examine data for statistical significance; $p < 0.05$ was considered significant.

RESULTS

During the lidocaine infusion, maternal arterial blood levels of lidocaine ranged between 0.81 and 4.60 $\mu\text{g/ml}$ with a mean value of 2.25 ± 0.13 (SE) $\mu\text{g/ml}$ (Table III). Foetal levels ranged between 0.65 and 4.0 $\mu\text{g/ml}$ with a mean value of 1.60 ± 1.1 $\mu\text{g/ml}$. The mean foetal maternal lidocaine ratio during the infusion was 0.76 ± 0.05 . The 135 minutes of lidocaine infusion did not significantly change maternal or foetal blood pressure, pulse rate, blood gases or acid-base status; nor did maternal cardiac output, stroke volume, total peripheral resistance, uterine blood flow or intra-amniotic fluid pressure vary significantly from control (Figure 1, Tables I and II).

DISCUSSION

We produced blood levels of lidocaine in the pregnant ewe comparable to those resulting from epidural anaesthesia in the human parturient during the first and second stages of labour. Such anaesthesia usually results in non-toxic blood levels of lidocaine (2–4 $\mu\text{g/ml}$).^{4,5} These blood levels are far less than those suggested to cause uterine artery constriction. For example, Gibbs and Noel² and Cibils³ demonstrated a vasoconstricting effect of both lidocaine and mepivacaine using

TABLE I
MATERNAL AND FOETAL CARDIOVASCULAR CHANGES DURING LIDOCAINE INTRAVENOUS INFUSION (0.25 MG/KG/MIN FOR INITIAL 15 MINUTES,
THEN 0.15 MG/KG/MIN) INTO A MATERNAL VEIN - 13 PREGNANT EWES

Maternal	Per cent change from control (mean $\pm$ S.E.)													
	Control	3 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	135 min	
Mean arterial blood pressure	78.1 $\pm$ 3.2	-0.8 $\pm$ 1.4	-0.1 $\pm$ 1.7	2.9 $\pm$ 1.5	0 $\pm$ 1.5	0.4 $\pm$ 2.1	1.9 $\pm$ 2.0	-0.9 $\pm$ 2.5	3.9 $\pm$ 1.6	5.9 $\pm$ 1.6	4.4 $\pm$ 1.6	6.2 $\pm$ 1.8	4.1 $\pm$ 2.5	
Pulse rate (beats/min)	108 $\pm$ 3.9	0 $\pm$ 2.4	0.5 $\pm$ 2.7	0.3 $\pm$ 2.5	-2.6 $\pm$ 2.1	0.7 $\pm$ 2.3	0.1 $\pm$ 2.2	-0.2 $\pm$ 3.2	-1.8 $\pm$ 2.2	-3.8 $\pm$ 3.6	-6.7 $\pm$ 2.7	-3.9 $\pm$ 3.6	-4.2 $\pm$ 4.7	
Cardiac output l/min	14.0 $\pm$ 1.1	—	—	—	—	-8.4 $\pm$ 4.4	-9.7 $\pm$ 3.5	-10.4 $\pm$ 5.1	-13.3 $\pm$ 3.8	-14.4 $\pm$ 4.0	-6.7 $\pm$ 4.2	-6.5 $\pm$ 4.5	-8.0 $\pm$ 4.7	
Uterine blood flow (ml/min)	656 $\pm$ 74.8	-1.8 $\pm$ 3.6	-0.9 $\pm$ 3.6	3.5 $\pm$ 4.0	-3.4 $\pm$ 4.6	-1.8 $\pm$ 3.9	-4.8 $\pm$ 3.8	-13.1 $\pm$ 7.2	-2.3 $\pm$ 5.3	-5.9 $\pm$ 5.2	-8.3 $\pm$ 6.2	-7.9 $\pm$ 7.1	-11.5 $\pm$ 7.9	
Stroke volume (ml)	132 $\pm$ 11.8	—	—	—	—	-9.5 $\pm$ 4.0	-6.7 $\pm$ 3.4	-7.8 $\pm$ 2.8	-8.0 $\pm$ 3.1	-9.1 $\pm$ 3.3	-0.6 $\pm$ 3.3	1.1 $\pm$ 3.6	-0.7 $\pm$ 4.4	
Total peripheral resistance (dynes/sec/cm ²)	487 $\pm$ 32.9	—	—	—	—	7.6 $\pm$ 6.5	10.8 $\pm$ 5.9	9.5 $\pm$ 5.4	16.2 $\pm$ 5.6	24.5 $\pm$ 8.2	12.0 $\pm$ 4.7	10.5 $\pm$ 4.7	6.7 $\pm$ 7.7	
Foetal	Control	3 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	135 min	
Mean arterial blood pressure (torr)	41.9 $\pm$ 2.3	-2.9 $\pm$ 1.7	-1.3 $\pm$ 1.3	-2.8 $\pm$ 2.4	-0.1 $\pm$ 3.0	-0.5 $\pm$ 3.1	3.1 $\pm$ 4.0	1.5 $\pm$ 3.6	1.3 $\pm$ 3.5	4.9 $\pm$ 3.2	1.3 $\pm$ 2.5	1.7 $\pm$ 4.2	-0.6 $\pm$ 2.7	
Pulse rate (beats/min)	162 $\pm$ 4.9	0.2 $\pm$ 1.4	2.9 $\pm$ 2.2	0.9 $\pm$ 3.3	1.7 $\pm$ 2.7	-1.2 $\pm$ 2.7	0.2 $\pm$ 3.1	-2.5 $\pm$ 1.7	-0.5 $\pm$ 3.1	-2.5 $\pm$ 3.6	-8.3 $\pm$ 3.3	-4.2 $\pm$ 2.7	-0.9 $\pm$ 3.9	

TABLE II
MATERNAL AND FOETAL BLOOD-GAS AND ACID-BASE VALUES DURING CONTROL PERIOD AND DURING INFUSION OF LIDOCAINE INTO THE EWE (MEAN $\pm$ S.E.)

		During lidocaine infusion									
Control		15	30	45	60	75	90	105	120	135	
pH (units)	Maternal	7.51±0.01	7.50±0.01	7.51±0.01	7.51±0.01	7.50±0.01	7.50±0.01	7.49±0.01	7.49±0.02	7.50±0.01	
	Foetal	7.34±0.04	7.32±0.11	7.33±0.02	7.32±0.02	7.32±0.02	7.31±0.02	7.31±0.02	7.31±0.02	7.31±0.02	
Pco ₂ (torr)	Maternal	29.9±1.0	29.4±0.8	28.8±1.1	29.5±0.7	28.7±1.2	29.8±0.7	30.4±0.9	30.2±0.7	30.2±0.8	
	Foetal	41.3±0.8	38.2±1.5	39.2±1.7	39.9±1.4	39.6±1.2	39.8±1.5	42.0±1.2	38.7±0.7	39.9±0.9	
Po ₂ (torr)	Maternal	105.8±5.8	104.4±4.8	105.4±4.1	102.7±3.6	104.5±3.9	104.0±4.5	105.2±5.2	102.9±4.3	104.3±4.3	
	Foetal	19.3±1.6	16.9±2.8	19.4±1.8	19.1±1.5	20.5±1.7	20.5±1.8	21.8±1.8	21.2±2.6	20.0±2.2	
Base excess (mEq/L)	Maternal	1.30±1.0	0.25±0.8	0.23±0.7	-0.3±0.8	0.9±0.72	0.14±0.6	-0.29±0.7	0.32±0.6	0.43±0.6	
	Foetal	-3.9±0.6	-5.3±0.6	-5.6±0.8	-5.5±1.0	-6.0±0.9	-5.82±1.2	-6.3±1.4	-6.9±1.5	-7.0±1.5	

TABLE III
MATERNAL AND FOETAL ARTERIAL LIDOCAINE CONCENTRATIONS AND RATIOS DURING LIDOCAINE INTRAVENOUS INFUSION (0.15 MG/KG/ML) INTO A MATERNAL VEIN 13 PREGNANT EWES

		15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	135 min
Maternal (μ gm/ml)		1.48 $\pm$ 0.26	1.73 $\pm$ 0.15	2.19 $\pm$ 0.18	2.49 $\pm$ 0.24	2.79 $\pm$ 0.13	2.22 $\pm$ 0.23	2.45 $\pm$ 0.09	2.41 $\pm$ 0.22	2.50 $\pm$ 0.27
Foetal (μ gm/ml)		1.09 $\pm$ 0.12	1.15 $\pm$ 0.04	1.30 $\pm$ 0.13	1.78 $\pm$ 0.20	1.79 $\pm$ 0.19	1.92 $\pm$ 0.19	1.67 $\pm$ 0.06	1.77 $\pm$ 0.45	1.95 $\pm$ 0.37
Foetal/maternal ratio		0.82	0.70	0.64	0.74	0.61	0.90	0.76	0.80	0.78

FIGURE 1. The effect of lidocaine infusion (0.15 mg/kg/min) for two hours on maternal blood pressure, pulse rate, cardiac output and uterine blood flow expressed as percent change from control.

human uterine artery segments obtained from caesarean hysterectomy specimens. However, the concentrations of local anaesthetic ranged from 400–1000 $\mu\text{gm/ml}$. This *in vitro* response was not seen with lower concentrations nor in uterine arteries taken from non-pregnant hysterectomy specimens, indicating that the response was dose-related and occurring only during pregnancy. Pre-treatment of the strips with phenoxybenzamine (an alpha-adrenergic blocker) did not abolish the vasoconstrictive response.

Griess, *et al.*,³ injecting 20, 40 and 80 mgm boluses of either lidocaine or mepivacaine into the dorsal aorta of eight anaesthetized pregnant ewes, found a dose-related transient (2 to 3 minutes) decrease in uterine blood flow and a simultaneous increase in intrauterine pressure. Uterine arterial blood levels were not measured. These investigators also infused lidocaine, mepivacaine, bupivacaine and procaine directly into the uterine artery of non-pregnant ewes. Calculated blood levels ranged between 4 and 200 $\mu\text{gm/ml}$ for lidocaine, mepivacaine and procaine and between 1 and 60 $\mu\text{gm/ml}$ for bupivacaine. The following uterine

arterial concentrations reduced mean uterine blood flow by 40 per cent: bupivacaine 5 $\mu\text{gm/ml}$, mepivacaine 40 $\mu\text{gm/ml}$, procaine 40 $\mu\text{gm/ml}$ and lidocaine 200 $\mu\text{gm/ml}$. Such enormously high concentrations could not occur during epidural anaesthesia in the absence of an intravenous injection.

Griess' data do suggest qualitative differences between various local anaesthetics. The ratio of the blood level causing a 40 per cent fall in uterine blood flow to the blood level usually found during epidural anaesthesia varied from 50 for lidocaine to five for bupivacaine and ten for mepivacaine. That is, bupivacaine, as used clinically, is more likely to reduce uterine blood flow than is mepivacaine which, in turn, may be more depressant than lidocaine. To suggest the absolute importance of this issue, a comparative study of the commonly used local anaesthetics over a wide range of blood levels found during obstetrical regional anaesthesia is essential.

Griess, *et al.* did not study the uterine blood flow changes at concentrations of local anaesthetics in the non-toxic clinical range. Our data indicate that a two-hour exposure to low concentrations of lidocaine in the pregnant ewe does not significantly decrease uterine blood flow or increase intra-uterine tone. In a recent study, Morishima and co-workers reported that in oxytocin-induced labour in ewes, lidocaine infusions producing blood levels of 4–9 $\mu\text{gm/ml}$, mildly to markedly increased uterine activity and intra-amniotic pressure while decreasing uterine blood flow.¹⁵ These drug levels marginally exceed those found during obstetrical anaesthesia and may be associated with central nervous system toxicity.¹¹

We previously demonstrated¹⁶ in the normotensive pregnant ewe that epidural anaesthesia with chlorprocaine resulting in an S_5 – T_{10} sensory level did not reduce uterine blood flow nor impair foetal well-being. This present study demonstrates that the blood level of lidocaine achieved during usual clinical anaesthesia also does not impair uterine blood flow. Thus epidural anaesthesia with lidocaine uncomplicated by hypotension should not significantly decrease uterine blood flow by either sympathetic blockade or by a direct, drug-induced increase in uterine vascular resistance.

SUMMARY

We infused lidocaine intravenously into 13 pregnant ewes at a rate sufficient to maintain plasma levels between 2–4 $\mu\text{gm/ml}$, which are those commonly seen with regional anaesthesia. These levels did not change maternal blood pressure, pulse rate, cardiac output, stroke volume, total peripheral resistance, uterine blood flow or intra-amniotic pressure. Foetal blood pressure and pulse rate remained stable as did both maternal and foetal blood gases and acid-base values.

RÉSUMÉ

Treize brebis en gestation ont reçu une perfusion intraveineuse de Lidocaïne. La perfusion était ajustée à un débit suffisant pour maintenir le taux plasmatique de Lidocaïne entre 2 et 4 $\mu\text{g/ml}$, taux que l'on rencontre habituellement en clinique sous anesthésie régionale.

Dans ces conditions, nous n'avons pas observé chez la mère de modifications de

la pression artérielle, de la fréquence cardiaque, du débit cardiaque, de la résistance périphérique totale, du débit sanguin utérin et de la pression du liquide amniotique. Du côté du fœtus la pression artérielle et la fréquence cardiaque sont demeurées stables. Les gaz artériels et l'équilibre acido-basique n'ont pas été modifiés, tant chez la mère que chez le fœtus.

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