

Bupivacaine-induced Cardiac Arrhythmias in Sheep

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Controversy persists about the cardiac toxicity of bupivacaine if accidentally administered intravenously during regional anesthesia. Using awake, unanesthetized sheep, we evaluated the cardiac effects of low and high equivalent doses of lidocaine and bupivacaine given intravenously over 10 s. All animals convulsed within 30 s of injections. Although both drugs significantly increased heart rate and systemic and pulmonary arterial blood pressure for up to 10 min, cardiac output was affected variably. The magnitude of hemodynamic changes that each drug produced did not differ significantly from each other at either dose level. However, of the sheep receiving intravenous lidocaine, none developed arrhythmias other than mild sinus tachycardia and minimal ST-T wave changes (which occurred in 25% of the animals). After intravenous bupivacaine injection, all sheep had transient changes on the EKG and/or arrhythmias (e.g., supraventricular tachycardia; atrioventricular conduction blocks; ventricular tachycardia; multiform premature ventricular contractions; wide QRS complexes; ST-T wave changes; and in one animal, fatal ventricular fibrillation). Normal sinus rhythm usually returned within 8-10 min. Arterial blood gas and acid-base values stayed within the normal range during the studies, and serum potassium did not change significantly from control. In conclusion, in conscious adult sheep, equivalent doses of lidocaine or bupivacaine produced similar central nervous system (CNS) toxicity when rapidly injected intravenously. In the absence of marked hypoxia, respiratory or metabolic acidosis, hyperkalemia, or hypotension, serious cardiac arrhythmias occurred after bupivacaine but not lidocaine. (Key words: Anesthetics, local: bupivacaine; lidocaine. Heart: arrhythmia. Toxicity.)

SEVERAL ANECDOTAL REPORTS indicate that after an accidental intravascular injection of a large dose of bupivacaine, seizures and cardiovascular collapse can occur almost simultaneously in some patients without apparent antecedent hypoxia.^{1,2,*} Moore *et al.*³⁻⁵ reported that

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** Allbright GA: Are long acting local anesthetics cardiotoxic? Abstracts of Scientific Papers, Annual Meeting of American Society of Regional Anesthesia, Monterey, California, 1982, p 90.

seizures caused by local anesthetics frequently are associated with severe hypoxia and acidosis. These authors proposed that cardiac arrest could be triggered by a delay in the proper treatment of such complications. They have since reported six cases of bupivacaine-induced convulsions that were managed promptly by ventilation with 100% oxygen without subsequent cardiac arrest.⁴

We investigated whether rapid intravenous (iv) injection of a long-acting local anesthetic such as bupivacaine would produce more significant cardiac abnormalities than clinically equivalent doses of lidocaine.

Methods

Following approval from the animal experimentation committee, 11 ewes, 2-3 years of age, had preparatory surgery while anesthetized with oxygen and halothane. Polyvinyl catheters (#8 Fr, 0.105 inches OD) were inserted into a femoral artery for continuous recording of blood pressure, into a femoral vein for drug injection, and into a carotid artery for obtaining blood samples. A flow-directed Swan-Ganz® catheter (#7 Fr), having a thermol-dilution thermistor and atrial and ventricular electrodes, was introduced through a neck incision via the internal jugular vein for measuring pulmonary arterial pressure, computing cardiac output and recording intracardiac changes on EKG. A tracheostomy was performed, and a #9.0 cuffed Portex tube was left in place to ensure easy accessibility for airway management and ventilation. Extradural skull screws, each 1.0 cm from the midline, were fixed into the parietal bone for continuous electroencephalographic recording. At least 24 h elapsed between these preparations and the study.

To establish a T4 sensory level in a 70-kg pregnant patient undergoing epidural anesthesia, the required dose is approximately 20 ml 2.0% lidocaine (5.7 mg/kg or 400 mg) or 20 ml 0.75% bupivacaine (2.1 mg/kg or 150 mg). While no studies have provided precise equivalent anesthetic doses for epidural administration of lidocaine or bupivacaine in sheep, studies with other local anesthetics⁶ have indicated that sheep probably have similar milligram-per-kilogram dosage requirements as humans. Therefore, our study animals received amounts of lidocaine or bupivacaine injected intravenously over 10 s ("low dose") that would ordinarily be used in humans. To exaggerate cardiac effects, we gave some animals twice this amount ("high dose"). The sequence of injection of local anesthetic was determined randomly, and on separate days one of the following dose regimens was given:

5.7 mg/kg 2.0% lidocaine ($n = 7$); 11.4 mg/kg 2.0% lidocaine ($n = 5$); 2.1 mg/kg 0.75% bupivacaine ($n = 9$); 4.2 mg/kg 0.75% bupivacaine ($n = 5$).

Although 11 animals were prepared for the study, the four dose regimens were not given to each ewe, as seen by the number in each group. Some animals were excluded from study when they developed pyrexia or pulmonary complications due to the tracheostomies.

To establish that these doses produced convulsions, we determined threshold doses in four ewes, using infusion rates of $4.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for lidocaine and $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for bupivacaine. These doses were administered on separate days, while the animals were awake, lying quietly, and breathing supplemental oxygen through tracheostomies. In sheep, the mean (\pm SE) doses that produced convulsions were $5.61 \pm 0.93 \text{ mg/kg}$ ($n = 4$) for lidocaine and $1.41 \pm 0.14 \text{ mg/kg}$ ($n = 4$) for bupivacaine.

After a 24-h recovery period, animals were vigorous and afebrile. Prior to study, baseline values for cardiovascular variables and arterial blood gas and acid-base status were determined during a 30-min control period, while the animals were awake and lying quietly, breathing room air or oxygen-enriched air ($\text{FI}_{\text{O}_2} 0.24$) to ensure normal resting Pa_{O_2} (75–100 mmHg). Arterial pH , Pa_{O_2} , and Pa_{CO_2} then were determined. Surface and intracardiac EKGs, electroencephalograph (EEG), and systemic and pulmonary arterial blood pressures were recorded continuously on a polygraph. Cardiac output was determined (by averaging readings of two or three injections) using a KMA (Kimray Medical Inc.) cardiac output computer every 10 min during the control period. To analyze arterial blood gases, acid-base status, serum potassium, and drug concentrations, we obtained blood samples at the onset of seizures; and at 1, 2, 3, 4, 5, 10, 15, 20, and 30 min after the iv injection of local anesthetic. Cardiovascular variables and EEG were recorded continuously, and cardiac output determinations were made to coincide with arterial blood sampling times when possible. Whole-blood drug concentrations were determined by a modification of our gas liquid chromatographic method.⁷ Approximately 90 s after injection of local anesthetic, 100% oxygen was administered. Thiopental, 1.0 mg/kg intravenously, was given to terminate seizures and was repeated if necessary; other cardiotoxic drugs were given as necessary for resuscitation.

We compared data using analysis of variance and unpaired Student's *t* test. A probability level of less than 0.05 was considered statistically significant.

Results

All animals convulsed within 30 s of a rapid iv injection, regardless of dose or drug. Although thiopental (1.0 mg/

kg intravenously) usually terminated both physical and electroencephalographic manifestations of the seizures, in approximately one-half of the studies, a second dose was necessary. There was no difference between local anesthetics regarding the necessity for a second dose of thiopental.

When lidocaine and bupivacaine were compared, the magnitude of hemodynamic effects did not differ at either dose. After low doses, heart rate increased to a maximum of 28% above control, regardless of drug, and after high doses, to a maximum of 81% above control for lidocaine and 54% for bupivacaine (fig. 1). The increase in heart rate was of sinus origin after lidocaine and of nodal or ventricular origin after bupivacaine.

Although mean arterial pressure increased to approximately 50% above control for both doses, after high doses, hypertension lasted longer (fig. 2). Pulmonary arterial pressure (systolic) increased to 109–169% of control, regardless of dose or drug.

During sinus rhythm, cardiac output did not change significantly from control, regardless of dose or drug. However, during ventricular tachycardia, cardiac output decreased precipitously.

For both anesthetics, drug concentrations in the blood were highest during seizures: for lidocaine, 17 $\mu\text{g/ml}$ (after the low dose) and 70 $\mu\text{g/ml}$ (after the high dose) (fig. 3); and for bupivacaine, 11 $\mu\text{g/ml}$ and 27 $\mu\text{g/ml}$, respectively (fig. 4). Also, within 3–5 min of injection, drug concentration in the blood decreased rapidly, *i.e.*, to less than 8 $\mu\text{g/ml}$ for lidocaine and to less than 3 $\mu\text{g/ml}$ for bupivacaine.

Marked hypoxia, hypercarbia, and respiratory or metabolic acidosis did not occur at any time. In fact, during seizures, when drug levels were the highest, animals spontaneously hyperventilated through the tracheostomy. The wide range of arterial blood gas and acid-base values are shown in table 1. The lowest Pa_{O_2} was 53 mmHg; the highest Pa_{CO_2} , 54 mmHg; and the lowest pH , 7.36. All measured serum potassium levels were normal and ranged from 3.4 to 4.4 mEq/l during seizures and ventricular arrhythmias.

Ventricular arrhythmias did not occur before iv injection or seizures. After lidocaine, no sheep had arrhythmias except for mild sinus tachycardia, which occurred in all sheep, and minimal changes in ST-T wave, which occurred in a few (fig. 5).

However, after bupivacaine, all sheep had transient changes on EKG and/or arrhythmias (table 2). The most common abnormality was widening of the QRS complex, which occurred in all animals regardless of dose. Other abnormalities included supraventricular tachycardia, atrioventricular conduction blocks, ventricular tachycardia, multifocal premature ventricular contractions (PVCs), and ST-T wave changes. ST-T wave depression

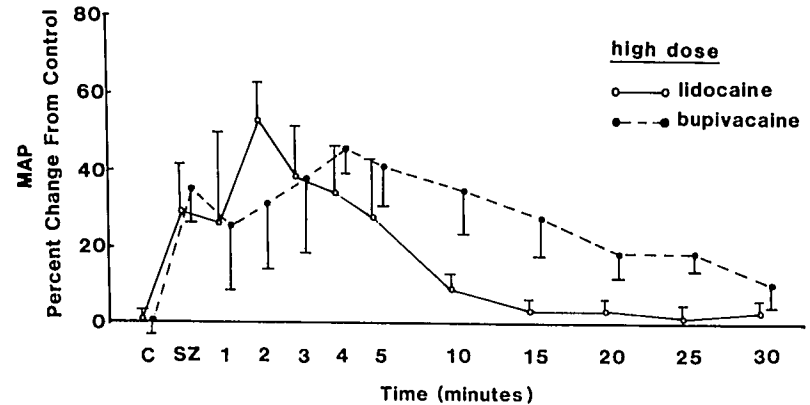
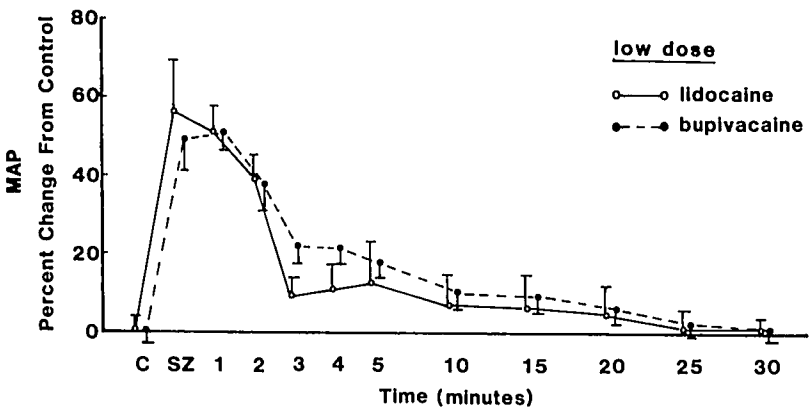
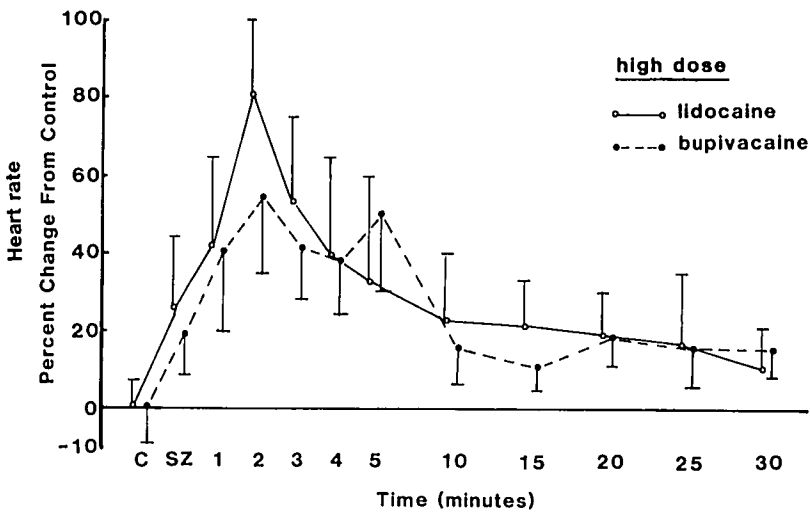
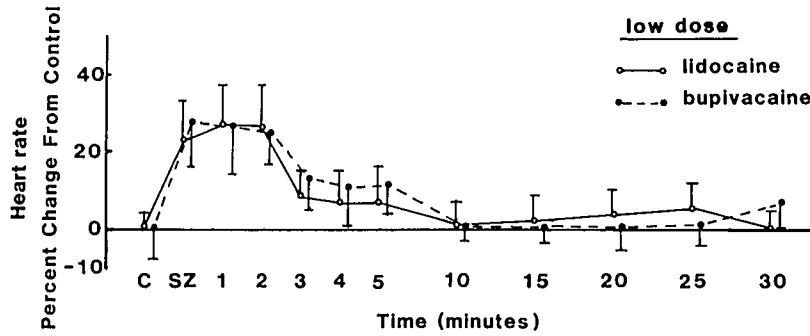


FIG. 1. Mean (\pm SE) change in heart rate after intravenous injection of lidocaine and bupivacaine. For lidocaine, the low dose was 5.7 mg/kg; the high dose, 11.4 mg/kg. For bupivacaine, the low dose was 2.1 mg/kg; the high dose, 4.2 mg/kg. There was no significant difference between changes caused by each drug.

FIG. 2. Mean (\pm SE) change in mean arterial pressure (MAP) after intravenous injection of lidocaine and bupivacaine at low and high doses.

FIG. 3. Mean (\pm SE) whole-blood drug levels of lidocaine after 10-s intravenous injections at low and high doses.

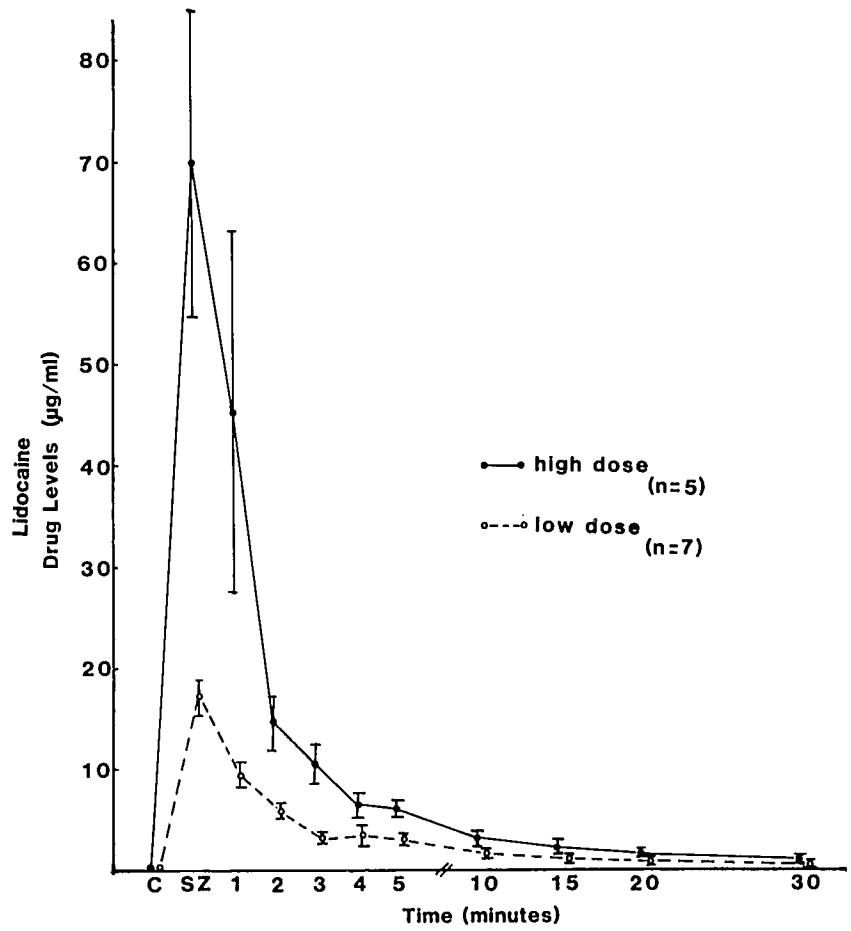


FIG. 4. Mean (\pm SE) whole-blood drug levels of bupivacaine after 10-s intravenous injections at low and high doses.

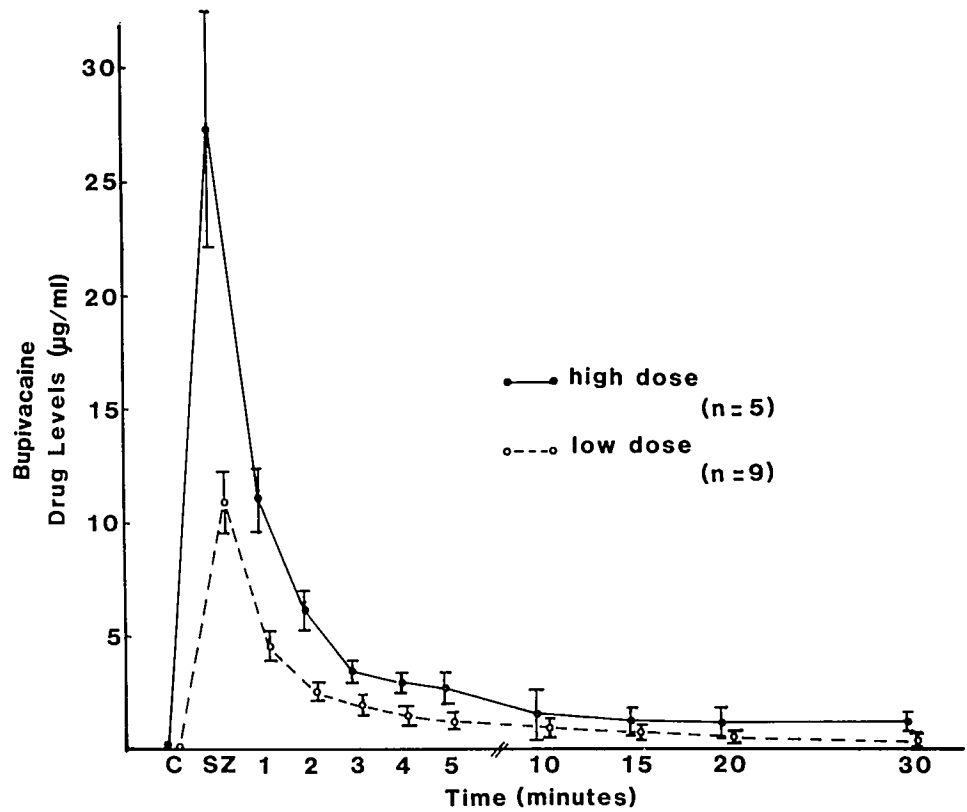


TABLE 1. Range of Arterial Blood Gas Values and Acid-Base Status of Sheep Receiving Lidocaine or Bupivacaine at Two Doses

	Lidocaine		Bupivacaine	
	Low Dose	High Dose	Low Dose	High Dose
pHa	7.41-7.67	7.42-7.70	7.37-7.64	7.36-7.59
PaO ₂ (mmHg)	60-447	53-388	68-460	59-342
PaCO ₂ (mmHg)	17-41	16-40	17-54	24-44
Base excess (mEq/l)	-0.7-7.5	1.6-7.1	-4.5-6.1	-0.2-7.4

of 2 mm from baseline control was considered significant (figs. 6-8).

Ventricular tachycardia, which developed after bupivacaine injection, usually lasted 3-10 s, and during these episodes cardiac output and blood pressure decreased acutely. An adequate pulse pressure then recurred spontaneously, even though the cardiac rhythm was comprised of multiform premature ventricular contractions (PVCs) or varying types of atrioventricular block with widened QRS complexes. In most of the sheep, the EKG returned to a sinus rhythm in 8-10 min, but in one animal given bupivacaine, ventricular tachycardia and fibrillation occurred. This 70-kg animal, one of the four sheep studied to determine convulsant dose, had received only 90 mg of bupivacaine (1.3 mg/kg). Prolonged resuscitation using

standard (ACLS) techniques of effective closed-chest cardiac massage and drugs was unsuccessful in restoring normal cardiac rhythm, as were administration of antiarrhythmic doses of lidocaine and electrical pacing with the Swan-Ganz® catheter.

Discussion

Most previous studies on cardiotoxicity of local anesthetics have been performed on isolated heart preparations^{8,††} or on anesthetized animals that were paralyzed and ventilated.⁹⁻¹³ To simulate more closely the clinical situation in which local anesthetic accidentally is injected

†† Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. *Regional Anesthesia* 8:55-61, 1981.

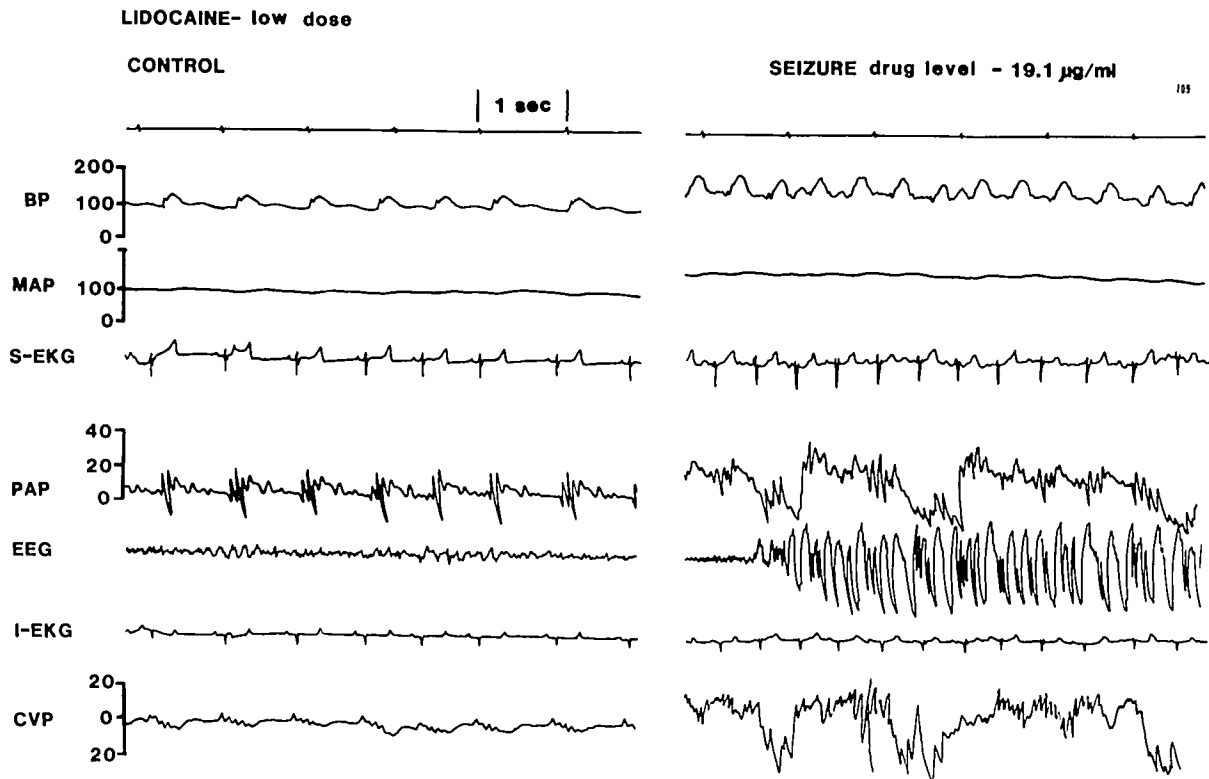


FIG. 5. In figures 5-8, a control tracing appears on the left, and changes are depicted on the right. After receiving lidocaine, 5.7 mg/kg iv ("low dose"), this animal had a blood drug concentration of 19.1 µg/ml at the time of seizure. Sinus tachycardia and hypertension are evident, as well as the onset of seizure. BP = blood pressure; MAP = mean arterial pressure; S-EKG = surface EKG; PAP = pulmonary arterial pressure; I-EKG = intracardiac EKG; CVP = central venous pressure.

intravenously, we studied awake, spontaneously breathing animals. We used concentrations and doses of lidocaine and bupivacaine that, when administered epidurally, produce the levels of sensory and motor blockade necessary for surgical anesthesia in humans.^{14-16,††} We considered these doses clinically equivalent for humans and sheep, and arbitrarily labeled them "low dose" for our study. In addition, to exaggerate cardiac effects, we gave some animals twice these amounts, which arbitrarily were labeled "high dose." If similar clinical doses of lidocaine and bupivacaine were equally cardiotoxic, we should have observed serious electrocardiographic changes after injection of each local anesthetic. However, after comparing electrocardiograms during low doses for both drugs, and even after comparing our high-dose lidocaine group with our low-dose bupivacaine group, we found that all sheep given bupivacaine had arrhythmias or changes on EKG, or both. Since, on a milligram-per-kilogram basis, the ratio of administered drugs in the latter comparison was 5.4 to 1, we actually administered lidocaine in an amount exceeding that known to cause CNS toxicity, *i.e.*, having a ratio of 4 to 1. Despite this higher dose of lidocaine, no serious arrhythmias were noted.

The doses of lidocaine and bupivacaine that we found caused convulsions (using conventional slow infusion) in

†† Ostheimer GW: Regional Anesthesia Techniques in Obstetrics. Publication BRN 2256. New York, New York, Breon Laboratories, Inc., 1980, pp 20, 24.

TABLE 2. Percentage of Sheep Having Changes on EKG and/or Arrhythmias after Lidocaine or Bupivacaine at Two Doses

Changes on EKG	Lidocaine		Bupivacaine	
	Low Dose (n= 7)	High Dose (n = 5)	Low Dose (n = 9)	High Dose (n = 5)
Sinus tachycardia	100	100	0	0
SV tachycardia	0	0	44	60
Atrioventricular blocks	0	0	56	60
Ventricular tachycardia	0	0	11	80
Multiform premature ventricular contractions	0	0	44	100
Wide QRS complexes	0	0	100	100
ST-T wave change	14	40	44	60

sheep, and their ratio (3.97 to 1), agree with data reported for other animals,^{12,17-20} for sheep,²¹ and for CNS toxicity in humans.^{22,23} Our chosen low dose for bupivacaine exceeded the convulsant threshold to a greater extent than our low dose for lidocaine. Possibly the severity of changes on EKG and/or arrhythmias would have been diminished if we had administered smaller doses of bupivacaine. However, as noted in the results, one of the four animals given bupivacaine by slow infusion to determine the dose causing convulsions had serious ventricular arrhythmias and died after receiving an iv dose of 1.3 mg/kg. Furthermore, de Jong *et al.*¹³ infused subconvulsant doses of bupivacaine or lidocaine in cats and found that cardiac arrhythmias were precipitated only with bupivacaine.

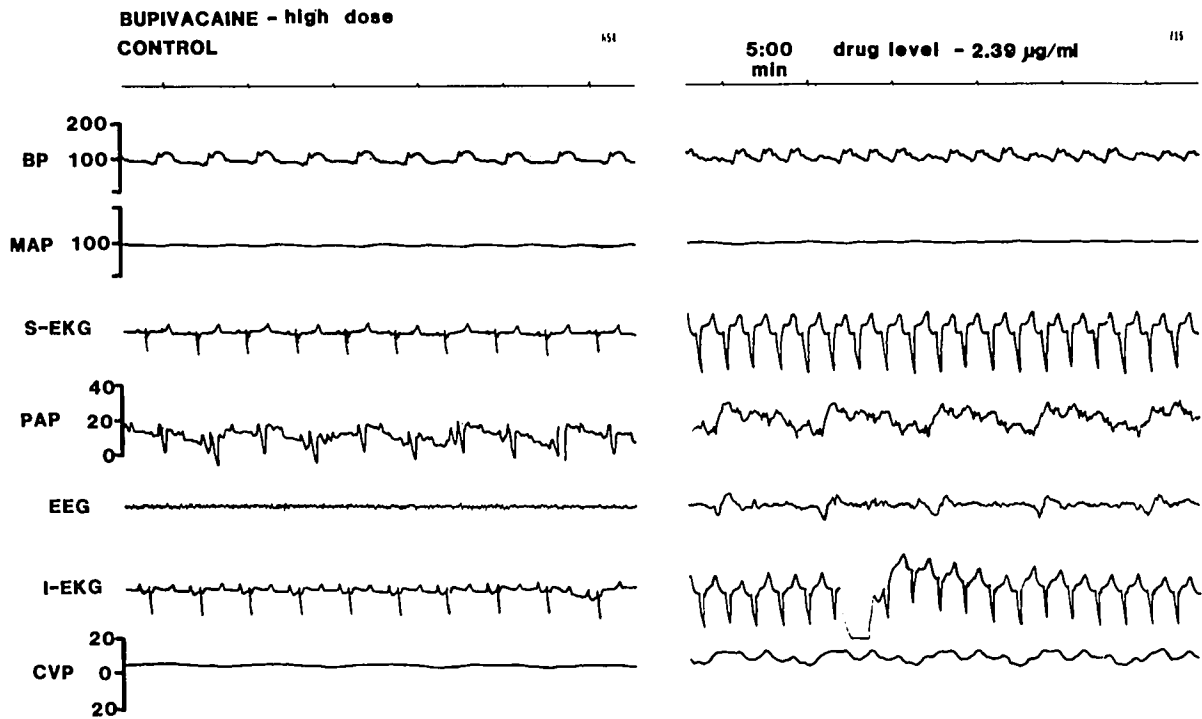


FIG. 6. Five minutes after receiving bupivacaine, 4.2 mg/kg iv ("high dose"), this animal had supraventricular tachycardia.

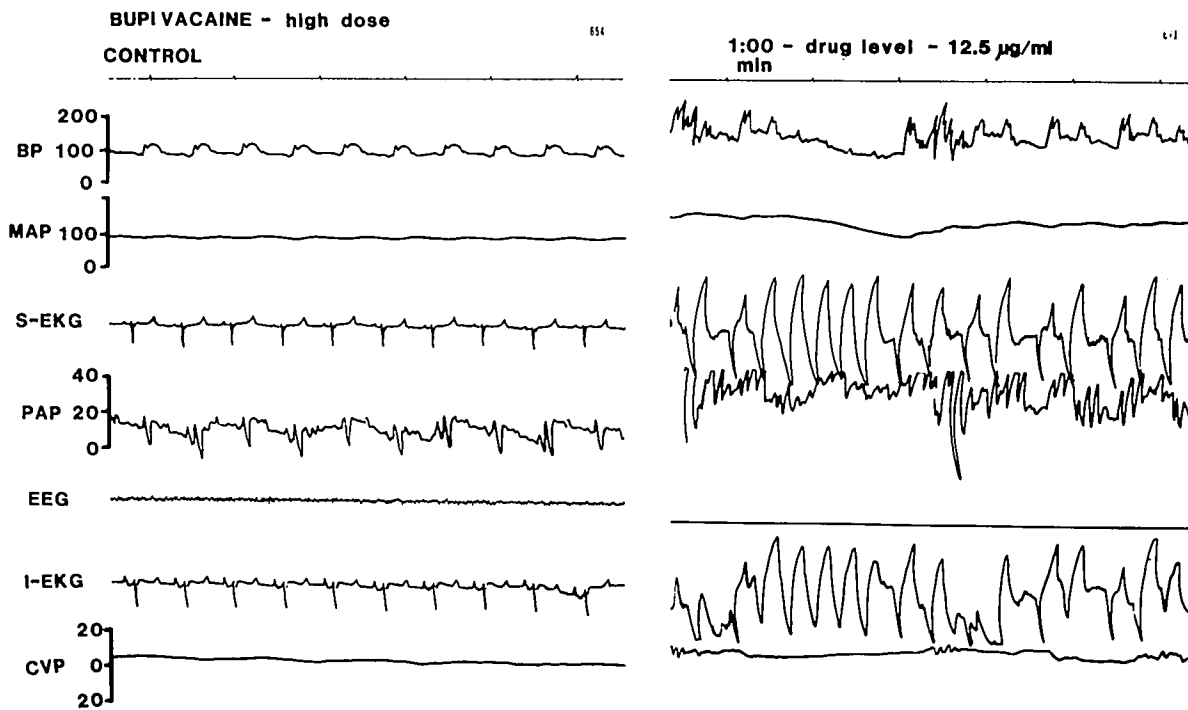


FIG. 7. One minute after receiving "high-dose" bupivacaine, this animal convulsed, then had ventricular tachycardia, followed by multiform premature ventricular contractions and intermittent atrial capture. Systemic pulse pressure fell acutely during this arrhythmia; however, initial blood pressure was elevated. Drug concentration in the blood was $12.5 \mu\text{g/ml}$; arterial P_{O_2} , 90 mmHg; P_{CO_2} , 43 mmHg; and pH , 7.44. The EEG tracing has been turned off on the right frame.

In our preparation, at the time of seizures, the whole blood concentrations and ratios of lidocaine and bupivacaine varied widely. In all sheep, the onset of seizures and simultaneous sampling of arterial blood occurred within 30 s of the end of local anesthetic injection, and seizures usually occurred sooner when higher doses were given. Possibly, our higher drug concentrations and variable ratios of lidocaine to bupivacaine resulted from minimal drug redistribution and metabolism. Volumes of

central compartment distribution may be different, and at very high levels these drugs may not obey first-order kinetics.

Most of the cardiovascular and hemodynamic effects of iv injection of toxic doses of local anesthetics were similar to those reported by other investigators.^{11,20,21,23,24} Changes in cardiac output varied, whereas mean systemic arterial pressure, pulmonary arterial pressure, and heart rate significantly increased from control for up to 10 min.

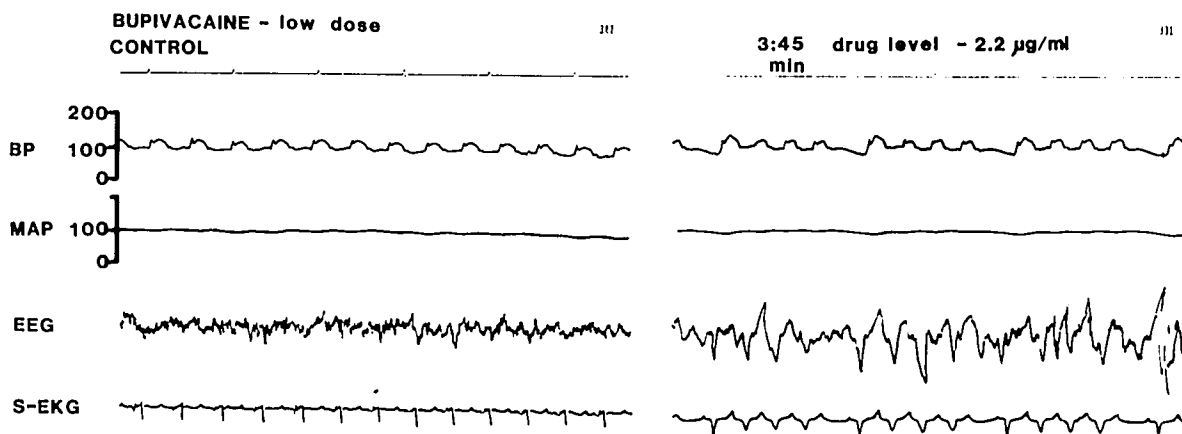


FIG. 8. After receiving "low-dose" bupivacaine, this animal had varying degrees of atrioventricular conduction block. Three minutes after injection, drug concentration in the blood was $2.30 \mu\text{g/ml}$, and atrial tachycardia with a 3:1 conduction was evident, along with widened QRS complexes.

When lidocaine and bupivacaine were compared, magnitude of cardiovascular effects did not differ significantly at either dose.

In a study using anesthetized and ventilated dogs, Liu *et al.*¹⁰ showed deterioration of hemodynamic status with increasing cumulative drug dose for all local anesthetics. They later reported that the acute cardiovascular toxicity of all amide anesthetics is similar and proportional to their *in vivo* anesthetic potency.¹¹ Because general anesthesia is known to modify the response of the circulation and central nervous system to stimuli,²⁵ our awake and unpremedicated sheep may be a more valid model for the clinical situation in which a seizure occurs after accidental injection of local anesthetic, which then is treated with an anticonvulsant. Liu *et al.*¹¹ concluded that if animals were ventilated to prevent hypoxia and acidosis following seizure, the ratio of cardiovascular to CNS toxicity for highly protein-bound and lipid-soluble agents such as bupivacaine would be similar to that of lidocaine. We were unable to confirm this finding, because our animals were neither hypoxic nor acidotic, but clearly experienced more cardiotoxicity with bupivacaine than with lidocaine. The different results may reflect variability between species or, more likely, our use of unanesthetized animals.

Block and Covino,^{§§} reporting on data from isolated whole rabbit hearts, showed that the depressant action of bupivacaine was about 10 times greater than that of lidocaine, with marked prolongation of intraatrial conduction, AV nodal conduction, intraventricular conduction, ventricular refractory period, and depression of ventricular contractility. In our intact sheep, we did not find significant decreases in cardiac output or sustained hypotension. On the contrary, most animals exhibited hypertension and adequate cardiac output, except during acute periods of serious ventricular arrhythmias. These effects were probably secondary to a stimulatory effect on the CNS,²⁴ which obviously could not be present in the isolated heart preparation.

We simultaneously used surface and intracardiac electrodes (incorporated into the Swan-Ganz[®] catheter) to obtain clear electrocardiographic recordings during seizures. Our finding of cardiac arrhythmias after iv bupivacaine injection has not been noted commonly. de Jong *et al.*^{13¶¶} reported that in anesthetized and ventilated cats, subconvulsant doses of bupivacaine and etidocaine precipitated cardiac arrhythmias and changes on EKG, whereas lidocaine did not. Most of these arrhythmias discontinued spontaneously, but persistent ventricular arrhythmias promptly converted to sinus rhythm after ad-

ministration of lidocaine (2.5 mg/kg) and diazepam. Similarly, in a case report of massive bupivacaine overdose in a patient, successful treatment included the use of lidocaine to correct ventricular tachycardia.² We did not administer lidocaine to treat bupivacaine-induced ventricular arrhythmias, except on one occasion, at which time it was not successful.

Because of increased muscle activity, seizures usually are associated with a marked increase in oxygen consumption, carbon dioxide production, and development of lactic acidosis.^{3,4,26} Albright*** believes that hypoxia, acidosis, and possibly hyperkalemia associated with seizures greatly may potentiate the severity and duration of cardiotoxicity of bupivacaine compared with that of lidocaine. He postulated that these conditions detrimentally affect plasma protein binding and lipid solubility, frequency-dependent conduction block, and myocardial uptake and redistribution. The use of a functioning tracheostomy in our animals prevented upper airway obstruction due to trismus and tetanic skeletal muscle spasm of the head and neck during seizures. In fact, most of the animals hyperventilated during seizures; and this hyperventilation, combined with administration of oxygen and rapid termination of tetanic seizure activity with thiopental, probably prevented marked hypoxia and hypercarbia, or metabolic acidosis. Even so, our animals experienced serious arrhythmias after bupivacaine. Perhaps with poor airway management, a lethal cardiac response would have occurred more frequently.

The occurrence of hyperkalemia may be another possible reason for the potentiation of cardiac problems reported after accidental intravascular injection of local anesthetic. Avery *et al.*,²⁷ studying dogs that were well oxygenated and ventilated, found that mild hyperkalemia produced cardiotoxicity at a significantly lower dose of bupivacaine than in the normokalemic state. Komai and Rusy⁸ identified mild hyperkalemia as one of the factors that potentiated the negative chronotropic effects of bupivacaine in the isolated, perfused rat heart model. Intravenous administration of succinylcholine for muscle relaxation and endotracheal intubation consistently causes transient elevations in serum potassium.²⁸ We were unable to document hyperkalemia as a cause of ventricular arrhythmias following bupivacaine injection. After initiating 100% oxygen and terminating the seizures with intravenous thiopental, we did not administer succinylcholine. While there were small fluctuations in serum potassium in some of our animals, these changes never exceeded 0.8 mEq/l. With normokalemia, this magnitude of change usually is not associated with deleterious cardiac effects.

We conclude that in unpremedicated conscious sheep

§§ Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. *Regional Anesthesia* 8:55-61, 1981.

¶¶ de Jong R, Davis NL: Treating bupivacaine arrhythmias: Preliminary report. *Regional Anesthesia* 6:99-103, 1981.

*** Albright GA: Are long acting local anesthetics cardiotoxic? Abstracts of Scientific Papers, Annual Meeting of Regional Anesthesia, Monterey, California, 1982, p 90.

having no upper airway obstruction, rapid intravenous administration of bupivacaine (convulsant doses or greater), but not lidocaine, produces severe cardiac arrhythmias. Ventricular arrhythmias seen after administration of bupivacaine were not attributable to marked hypoxia, hypercarbia, acidosis, hyperkalemia, or hypotension.

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