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Toxicity and Resuscitation in Lidocaine- or Bupivacaine-infused Cats

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Controversy persists surrounding the relative safety of bupivacaine compared with lidocaine especially with regard to its cardiovascular toxicity and the ability to resuscitate following such occurrences. The margin of safety between seizure onset and cardiovascular collapse was compared in lightly anesthetized and ventilated cats given an equipotent infusion of either lidocaine or bupivacaine (N = 10 for each group). The infusion rates were 4 mg · kg^{-1} · min^{-1} bupivacaine or 16 mg · kg^{-1} · min^{-1} lidocaine. Onset of electrical seizure activity occurred at about the same time in both groups and was defined as the central nervous system (CNS) toxic end point. The infusion continued until the mean arterial pressure reached 10 mmHg (cardiotoxic end point). Despite the early occurrence of electrocardiographic changes in the bupivacaine group, mean arterial pressure was greater and sustained significantly longer (4.9 ± 1.3 min; mean ± SD) with this drug compared with lidocaine (3.0 ± 0.6 min) ($P < 0.005$). Using the blood pressure criterion for defining cardiovascular (CV) collapse, the CV/CNS toxicity ratio for drug dosage was 4.0 with lidocaine and 4.8 with bupivacaine. The use of a standardized resuscitation protocol made it possible to compare the ability to resuscitate animals in each group. Despite very high plasma local anesthetic concentrations, all lidocaine-infused animals were quickly resuscitated (4.4 ± 3.0 min; mean ± SD). The resuscitation time for the bupivacaine group (5.4 ± 2.4 min) was similar. Two cats in the bupivacaine group could not be brought to resuscitation criterion, a difference, however, that was not statistically significant. (Key words: Anesthetics, local: bupivacaine; lidocaine. Brain: seizures. Heart: cardiac arrest. Toxicity: local anesthetics.

SINCE THE ORIGINAL clinical report by Prentiss[1] and the editorial by Albright in 1979,[2] much research has been focused on the relative systemic toxicity of the newer amide local anesthetics such as bupivacaine compared with lidocaine. Some studies have indicated that the toxicity parallels the anesthetic potency for these drugs.[3,4] Other investigators have concluded that bupivacaine has a greater cardiovascular toxicity and/or a lesser margin of safety.[5–8] Of particular concern have been clinical reports of difficult if not impossible resuscitation efforts following cardiovascular collapse with bupivacaine. Although a number of studies have commented on similar difficulty with resuscitations in laboratory models,[7,8] only the report by Kasten and Martin[9] has claimed success in resuscitating animals following cardiovascular collapse induced with bupivacaine.

In this study we compared the central nervous system (CNS) and cardiovascular (CV) toxicity of lidocaine with that of bupivacaine with the use of a ventilated cat model. The local anesthetics were infused at rates chosen to model accidental intravenous injections delivered at a rapid rate. In addition to comparing the toxicity of these agents, we compared the ability to resuscitate cats after a potentially lethal dose of either agent.

Methods

Twenty healthy cats of either sex with weights between 2.9 and 4.3 kg were alternately assigned to either the lidocaine or bupivacaine group. All animals were fasted the night before the study, although *ad libitum* water was available. Both groups (N = 10) were well matched with respect to weight and other variables (table 1).

After each animal was placed in a restraining bag, anesthesia was induced with halothane in N_2O and O_2 delivered via mask. The trachea was intubated with a 3.5–4.0 mm internal diameter cuffed endotracheal tube, and anesthesia was maintained with 1% halothane in 70% N_2O and 30% oxygen. Neuromuscular relaxation was initiated with pancuronium bromide 0.1 mg/kg, and ventilation was controlled with a small animal ventilator (Harvard®, model 670).

Lead II of the ECG and the right and left frontooccipital EEG were recorded continuously. Esophageal temperature was measured (Yellow Springs Instruments) and maintained at normal levels with warming blanket and radiant heating lamp. End-tidal CO_2 ($P_{ET_{CO_2}}$) was recorded (Beckman® CO_2 analyzer, model LB-1) and in conjunction with blood gas determinations used to adjust ventilation.

A right femoral cutdown was performed for placement of arterial and central venous catheters. The arterial catheter was used for pressure recording (Statham®, P23AA) and blood sampling. The central venous catheter was placed into the right atrium with the use of the ECG for positioning.[10] This catheter was used for local anesthetic infusion and for administration of resuscitation drugs. Arterial pressure, ECG, EEG, and $P_{ET_{CO_2}}$ were recorded on a paper strip chart recorder (Grass®, 7P5 polygraph) as well as on magnetic tape (Ampex®, FT-1300).

Following placement of catheters, halothane was discontinued (ventilation with 70% N_2O and 30% O_2 continued), pancuronium bromide 0.2 mg administered, and

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TABLE 1. Control Values

	Wt. (kg)	Temp. (°C)	Hct. (%)	K^+ (mEq/l)	Tot. Protein (g/dl)	Alb. (g/dl)	pH	$Paco_2$ (mmHg)	Pao_2 (mmHg)
Lidocaine	3.40 ± 0.39	37.4 ± 0.4	34 ± 7	3.9 ± 0.5	5.4 ± 0.4	2.6 ± 0.2	7.36 ± 0.02	37 ± 2	133 ± 20
Bupivacaine	3.34 ± 0.43	37.7 ± 0.6	36 ± 5	4.3 ± 0.5	5.8 ± 0.9	2.5 ± 0.4	7.36 ± 0.02	37 ± 1	143 ± 14

Mean ± SD. For each group N = 10.

the animal left undistributed for at least 20 min to allow time for halothane elimination. After stable vital signs and satisfactory blood–gas values were confirmed (Radiometer®, BMS 3 Mk2 with PHM 71 Mk2 acid-base analyzer), drug infusion was begun with either lidocaine 2.0% at 16 $mg \cdot kg^{-1} \cdot min^{-1}$ or bupivacaine 0.5% at 4 $mg \cdot kg^{-1} \cdot min^{-1}$ with the use of a motor-driven syringe-type infusion pump (Sage®, 255-1). Elapsed time until first spike activity on the EEG was noted. The infusion was stopped when mean arterial pressure (MAP) reached 10 mmHg. At this point no intervention was instituted, although ventilation was continued.

After exactly 3 min the resuscitation sequence was begun. The protocol used is a modification of one published previously.[11] This involved a standard sequence of increasing the minute ventilation approximately 30%, administering 100% O_2, closed-chest cardiac compression, and the following drugs in a fixed dosage combination: epinephrine 10 μg/kg, $CaCl_2$ 10 mg/kg, and $NaHCO_3$ 1 mEq/kg. If no rhythm was present after 2 min, the above sequence was repeated at 1–2-min intervals until a spontaneous ECG rhythm returned. In the beginning of the study, externally applied direct current cardioversion (15–20 J) was used in an attempt to obtain a pressure generating rhythm; however, this was soon discontinued, since all animals spontaneously reverted to a cardiac rhythm with ventricular complexes. Cardiac compressions were continued until self-sustained pulsatile flow returned. At this point, boluses of epinephrine 10 μg and occasionally atropine 0.1 mg were given to increase perfusion pressure and/or heart rate as rapidly as possible. Resuscitation was considered complete when a self-sustained mean pressure of 100 mmHg was achieved. Blood gas values then were corrected as rapidly as possible by adjusting minute ventilation and administration of bicarbonate if necessary. Blood was drawn for determination of local anesthetic concentrations before drug infusion, at the time of first spike activity on the EEG, when MAP reached 10 mmHg, when resuscitation criterion was achieved, and at 10 min intervals for the next 40 min. Local anesthetic plasma concentrations were determined with the use of gas chromatography.[12] The total amount of blood drawn for all determinations ranged between 6 and 10% of each animal's total blood volume and was replaced with lactated Ringer's solution in a volume approximately equal to three times the removed blood volume.

The data were analyzed by Fisher's Exact Test and unpaired Student's *t* test. A *P* value of less than 0.05 was considered statistically significant.

Results

Shortly after beginning the drug infusion, many animals demonstrated an increase in mean arterial pressure. This was more pronounced in the bupivacaine group than in the lidocaine group. The lidocaine-infused animals usually did not demonstrate this initial increase in blood pressure. Mean arterial pressure decreased earlier and more rapidly with lidocaine infusion, although heart rate was faster in this group compared with the bupivacaine group. Mean arterial pressure and heart rate changes are illustrated in figure 1.

The first spike activity evident on the EEG occurred at 0.8 ± 0.3 min (mean ± SD) following the beginning of lidocaine infusion compared with 1.1 ± 0.3 min with bupivacaine. This difference was not statistically significant. Although the first occurrence of spike wave activity was taken as the CNS toxic end point, in almost all cases this was followed within seconds by the typical high-amplitude, high-frequency bursts characteristic of local anesthetic-induced seizures (Fig. 2*D*). One cat in each group progressed directly to a suppressed EEG pattern without evidence of seizure activity. The progressive EEG changes leading up to seizure discharges were not consistently different in either group.

The cardiovascular end point (MAP = 10 mmHg) was reached at 3.0 ± 0.6 min after starting the infusion in the lidocaine group and at 4.9 ± 1.3 min with bupivacaine infusion. This difference is statistically significant ($P < 0.005$).

Although greater time was required to reach the cardiotoxic end point in the bupivacaine group, ECG changes occurred earlier and progressed more quickly in the animals of this group. The changes became evident before the onset of seizure activity on the EEG and usually were characterized by large changes in voltage and widened QRS complexes. The lidocaine group only rarely showed evidence of altered ECG patterns before seizure discharges; when these did occur they were limited to changes in voltage and ST-T wave conformation (fig. 2).

Although the time course of ECG changes was different in the two groups, the observed changes characteristically followed a similar pattern. First, alteration in QRS configuration and voltage became evident. This was followed by widening of the QRS, which often resembled ventricular tachycardia (fig. 2*B*), although P waves still were present as became evident when heart rate began to slow. Progressive A-V block eventually resulted in complete A-V dissociation. Finally, ventricular complexes ended with or without continued P waves.

All animals became asystolic either shortly before or after mean arterial pressure equaled 10 mmHg. Further reductions in blood pressure occurred slowly, even in the absence of any cardiac output as inferred from electrical silence on ECG and a nearly flat end-tidal CO_2 trace.

The mean convulsive dose was 11.7 ± 4.6 mg/kg (mean ± SD) lidocaine and 3.8 ± 1.0 mg/kg bupivacaine. The mean cardiotoxic dose as defined in this study was 47.3 ± 8.6 mg/kg lidocaine and 18.4 ± 4.9 mg/kg bupivacaine. Local anesthetic plasma levels are reported in table 2. As can be seen, these levels were very high at the end of drug infusion but decreased dramatically by the time resuscitation was complete. This initial rapid decline in blood levels presumably represents dilution and redistribution of the local anesthetic during the resuscitation period.

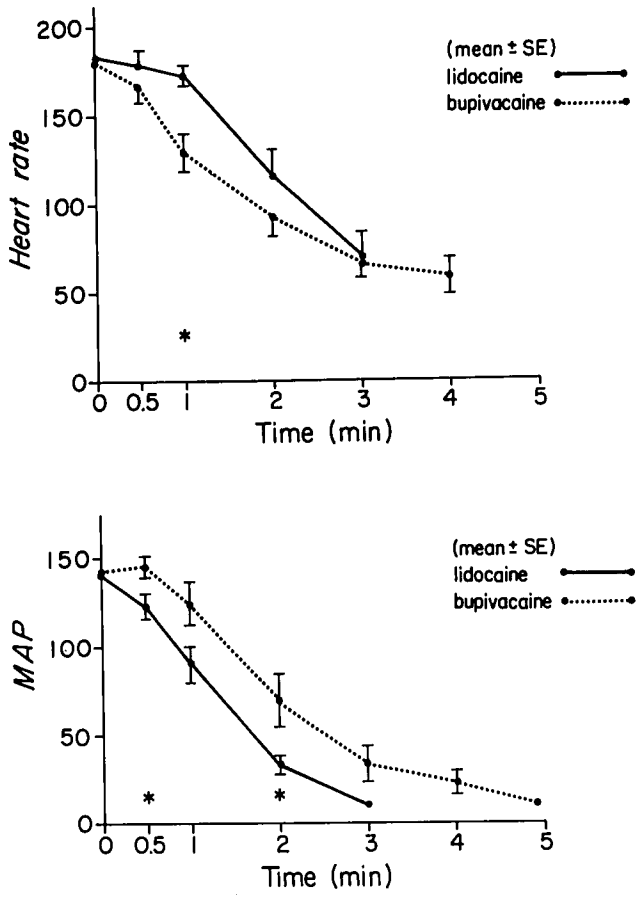

FIG. 1. Local anesthetic-induced changes in mean arterial pressure (MAP) and heart rate are shown for each group during drug infusion, which was begun at time 0. Intergroup differences are significant ($P < 0.05$) at times indicated with an asterisk (*).

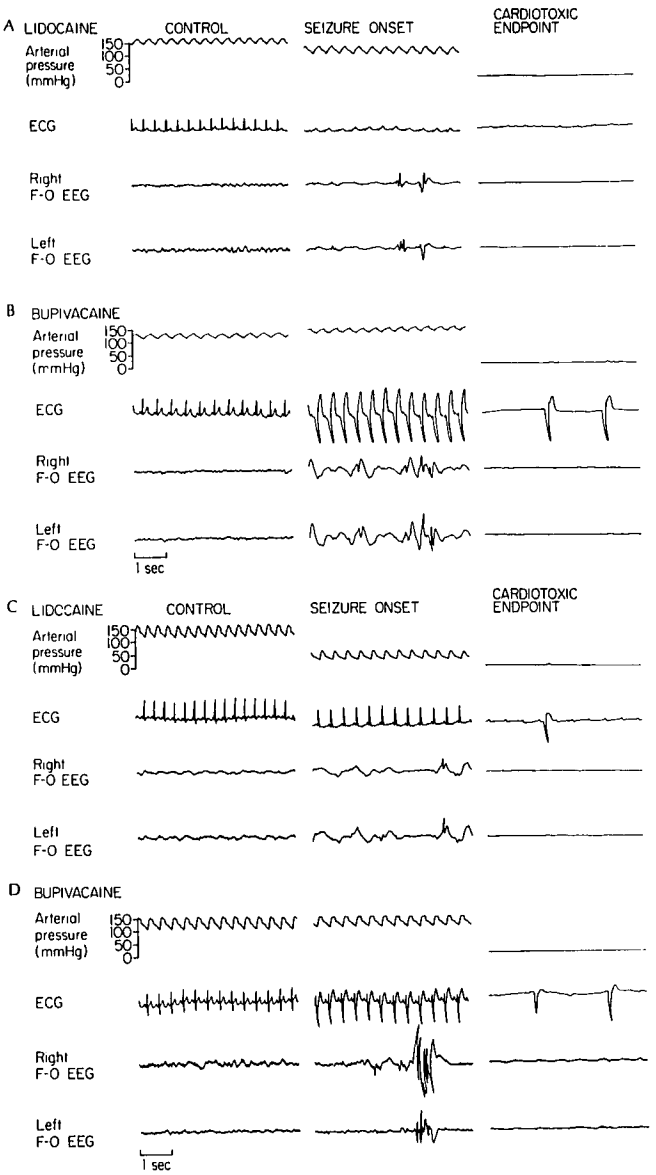

FIG. 2. Illustrated are the arterial pressure, ECG, and EEG traces of two lidocaine- and two bupivacaine-infused animals immediately before drug infusion, at the time of first spike activity on the EEG, and at the cardiotoxic end point (MAP = 10 mmHg). Significant conduction abnormality is evident in the bupivacaine-infused animals at seizure onset (*B* and *D*) despite little change in arterial pressure. Much less ECG alteration is seen in the lidocaine animals at this time, even though arterial pressure is already depressed (*A* and *C*). All animals became asystolic either before MAP = 10 mmHg (*A*) or soon thereafter.

Ability to resuscitate animals in each group was assessed by comparing the resuscitation times as well as the number

TABLE 2. Local Anesthesia Plasma Levels

	Seizure Onset	CV End Point	Resuscitation Criterion	Minutes Postresuscitation 10	20	30	40
Lidocaine	139.9 ± 68.6	402.4 ± 95.1	45.4 ± 18.1	21.9 ± 8.6	15.8 ± 5.0	10.9 ± 4.0	9.0 ± 3.5
Bupivacaine	37.0 ± 11.3	110.2 ± 24.6	13.1 ± 4.4	8.4 ± 2.0	6.0 ± 1.0	5.2 ± 0.7	4.8 ± 1.0

Mean ± SD, μg/ml.

of successful resuscitations in each group. The time to return of spontaneous ECG rhythm as well as the time required for a self-sustained arterial pressure of ≥100 mmHg to be achieved is illustrated in table 3. There was no significant difference between groups in either of these measures.

All animals showed a spontaneous return of ventricular rhythm on the ECG; however, two animals infused with bupivacaine could not be brought to resuscitation criterion. Failure to resuscitate these two animals did not reach statistical significance ($P < 0.24$). All of the lidocaine-infused animals were resuscitated successfully.

Discussion

Despite a considerable amount of research by numerous investigators directed at the question of relative local anesthetic toxicity and safety, the results are confusing and final answers remain elusive. Differences in animal models, drug infusion schedules or administration rates, the presence or absence of general anesthetic agents, and whether ventilatory support was provided are some of the more obvious factors that may influence the results obtained.

The design of this study was directed at two fundamental questions: first, to determine the margin of safety between CNS toxicity and cardiovascular collapse for lidocaine and bupivacaine, and, second, to address the question of whether it is more difficult to resuscitate following lethal doses of bupivacaine compared with lidocaine.

The cat was chosen as the experimental species, since the author had familiarity with an effective resuscitation protocol in this animal, which is similar to human cardiopulmonary resuscitation methods.[11] In order to approximate the worst possible clinical scenario of inadvertent intravenous injection, a very rapid infusion rate was chosen. Previous local anesthetic toxicity studies used cumulative doses or infusion rates that were slower than those that might be used clinically. The dosage rates employed here are equivalent to injecting 1 ml/s of either lidocaine 2% or bupivacaine 0.5% in a 75-kg patient. The local anesthetic was infused directly into the right atrium to minimize dilution effects and to eliminate variability due to possible differences in venous flow rates. In order to eliminate the confounding variables of hypoxia, hypercarbia, and acidosis, the animals were ventilated during the study and blood gases closely controlled. The presence of 70% N_2O during drug infusion was felt necessary to provide sedation for these paralyzed and ventilated animals.

TABLE 3. Resuscitation Times

	Time to Return of ECG Rhythm	Time to Resuscitation Criterion
Lidocaine	3.5 ± 2.4	4.4 ± 3.0
Bupivacaine	2.2 ± 0.7	5.4 ± 2.4

Mean ± SD in minutes.

A fundamental assumption in this study is that the relative potency of bupivacaine and lidocaine is 4:1, a value derived from both *in vitro*[13,14] as well as *in vivo* data.[15] This relative potency ratio is also one that has been implicit in many studies of local anesthetic toxicity. Since equipotent infusion rates were used, the similar latency to seizure onset in both groups supports the conclusion that CNS toxicity parallels anesthetic potency. The same conclusions have been drawn by other investigators.[5,16,17]

The seizurogenic doses in this study are less than those reported by others using slower infusion rates[5,16] or cumulative doses.[17] Malagodi[18] has pointed out the importnace of infusion rate on CNS toxicity of local anesthetics. The rapid infusion rates resulted in higher plasma concentrations from a lower dose infused, presumably because equilibration was not allowed to occur. Infusion rates in the present study were four times those used by Munson *et al.*[16] or de Jong *et al.*,[5] and the seizurogenic plasma level was substantially higher than in either of their studies. The plasma lidocaine to bupivacaine ratios, however, were comparable; 3.8 in this study compared with 4.0 reported by Munson and 5.4 in the study by de Jong *et al.*

Much less agreement is found in the literature with regard to the CV toxicity of these local anesthetic agents. Liu *et al.*,[4] using cumulative doses in pentobarbital-anesthetized and ventilated dogs concluded that the cardiotoxic doses for lidocaine and bupivacaine were similar to their intrinsic potencies. In that study, the cardiotoxic end point was defined by hypotension and asystole. Kotelko *et al.*,[7] using awake tracheostomized sheep given a "rapid" injection of 2.1 mg/kg bupivacaine or 5.7 mg/

kg lidocaine concluded that bupivacaine had greater cardiac toxicity, since serious arrhythmias were observed with that drug but not with lidocaine. De Jong *et al.*[5] also had concluded that bupivacaine was more cardiotoxic, based on its observed greater arrhythmogenicity in cats ventilated with 70% N_2O.

Morishema *et al.*[19] reported a narrower margin of safety between seizures and cardiovascular collapse in awake sheep infused with bupivacaine compared with a group infused with lidocaine. Since that study as well as the current one used local anesthetic infusions to the point of CNS toxicity and cardiovascular collapse, the different results obtained are of interest. Species differences as well as differences in dosage rates (2 $mg \cdot kg^{-1} \cdot min^{-1}$ lidocaine or 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ bupivacaine) may be responsible for the results obtained. Perhaps more important, however, is that the sheep were not ventilated and may have become acidotic and hypoxic following the onset of convulsions and respiratory arrest. This may well have accelerated the occurrence of cardiovascular collapse and narrowed the margin between CNS and CV toxicity, especially in the bupivacaine group.[8,20]

In this study the CV toxic end point was chosen based on a blood pressure criterion (MAP = 10 mmHg). With the use of this definition, the margin of safety between CNS and CV end points actually was found to be greater for bupivacaine compared with lidocaine. The ECG changes that occurred at approximately convulsive doses of bupivacaine but only later with lidocaine are in marked contrast to the observed blood pressure changes (fig. 2). Clearly, the definition of cardiac toxicity is an important one and must be specified precisely in studies of this type.

At equivalent times during drug infusion the arterial pressure was greater in the bupivacaine group, which resulted in the longer time required for the CV end point to be reached (fig. 1). Similar observations have been reported by de Jong *et al.*[5] and can be seen in the results of Kotelko *et al.*[7] in their "high-dose" group. The greater arterial pressures observed in the bupivacaine animals, despite abnormal cardiac electrical activity, is interesting especially in view of the findings from isolated heart preparations that bupivacaine has approximately 20 times the myocardial depressant properties of lidocaine.† Local anesthetic stimulation of the CNS has been proposed as the mechanism responsible for this paradoxic effect.[21]

The cardiotoxic doses determined in this study are extremely high and certainly much greater than would be expected for human toxic doses. This may be due in part to the cardiotoxic end point chosen as well as the fact that drug administration continued, beyond what may have been potentially lethal doses, until MAP had reached 10 mmHg. It is interesting to speculate at which point the observed cardiovascular changes would have been fatal (without continued drug infusion). Presumably the greater blood pressures of the bupivacaine animals would have allowed redistribution of local anesthetic and spontaneous recovery even later into the infusion than with the lidocaine group. In this sense it may be that the margin of safety for bupivacaine is similar if not greater than that of lidocaine, at least in this animal model.

Particular concern has been expressed in regard to the reported cases of prolonged and difficult, if not impossible, resuscitations following cardiovascular collapse associated with the long-acting amide local anesthetics.[2] Studies in which attempts were made to resuscitate animals following cardiovascular collapse induced with bupivacaine have commented on similar difficulty with resuscitations.[7,8] Kasten and Martin[9] have reported the ability to resuscitate dogs following bupivacaine-induced cardiovascular collapse using open-chest cardiopulmonary resuscitation (CPR). Conclusions about the relative difficulty of such resuscitations, however, cannot be drawn, since a similar group arrested with a different local anesthetic was not included.

The study reported here directly compares the ability to resuscitate cats following massive and potentially lethal doses of lidocaine or bupivacaine using a closed-chest CPR technique. It is important to note that since the bupivacaine group was infused for a significantly longer time, this group actually received a relatively greater amount of drug than did the lidocaine-infused animals (based on the 4:1 potency ratio). All animals had a return of spontaneous ECG rhythm, although two of the bupivacaine animals could not be brought to criterion blood pressures. The reason for this is not clear, but since these animals received 1.6 times the equivalent lidocaine dose, one might expect more difficulty with their resuscitations. For the 20 animals in this study, the inability to resuscitate two in one group did not reach statistical significance ($P < 0.24$). Similar resuscitation times for each group further support the conclusion that it is not more difficult to resuscitate cats following potentially lethal doses of bupivacaine (table 3).

In summary, this study, using continuously ventilated cats anesthetized with 70% N_2O, found that bupivacaine has a greater arrhythmogenic effect although a lesser hypotensive effect than lidocaine. In clinical reports of bupivacaine cardiotoxicity, ventricular tachycardia or ventricular fibrillation was the most frequently reported rhythm.[2,22–24] It may be that bupivacaine-induced arrhythmias are more severe in the human or that the rapid occurrence of hypoxia and acidosis that has been demonstrated to follow local anesthetic-induced convulsions[25] contributed to early cardiovascular collapse. Continuous

† Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. Regional Anesthesia 6:55–61, 1981

ventilatory support in our animals may have afforded significant protection, especially since the presnce of hypoxia and acidosis has been associated with greater bupivacaine cardiotoxicity.[8,20] The extrapolation of animal studies to clinical practice must be done cautiously, but it would seem prudent to establish early and effective ventilation in cases of suspected local anesthetic toxicity and in the event of cardiovascular collapse to rapidly establish satisfactory perfusion pressures with pharmacologic support as necessary.

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