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The Influence of Serum Potassium on the Cerebral and Cardiac Toxicity of Bupivacaine and Lidocaine

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The influence of hyperkalemia on the central nervous system and cardiac toxicity of bupivacaine and lidocaine was studied in open-chested mechanically ventilated dogs. The seizure and cardiotoxic doses of intravenously administered lidocaine and bupivacaine were determined in two separate groups of normokalemic (2.7 ± 0.05 SEM mEq/l) dogs. In the case of both anesthetics, the cardiotoxic dose was found to be approximately four times the seizure dose. Under conditions of hyperkalemia (5.4 ± 0.08 SEM mEq/l), however, the cardiotoxic doses of both anesthetics were decreased significantly to approximately two times the seizure dose. Hyperkalemia did not change the seizure dose for either anesthetic. The cardiac to seizure dose ratio was decreased significantly for bupivacaine but not for lidocaine. The results of this study suggest that hyperkalemia enhances the cardiotoxic effects of both lidocaine and bupivacaine, with this enhancement being more pronounced in the case of bupivacaine. (Key words: Anesthetics, local: bupivacaine: lidocaine. Brain: seizure. Ions: potassium. Toxicity: local anesthetics.)

IN A RECENT STUDY of local anesthetic-induced convulsions in spontaneously breathing mice,[1] de Jong and Bonin propose that the gap between the convulsant and lethal doses of lidocaine, chloroprocaine, and bupivacaine is quite narrow. Similarly, clinical reports[2] have indicated that cardiac arrests associated with the injection of long-acting local anesthetics have occurred almost simultaneously with seizure activity. However, data from animal studies in which ventilation was supported mechanically suggest that cardiovascular function is well preserved in the presence of convulsant doses of bupivacaine.[3,4]

In an attempt to identify factors that may potentiate the cardiovascular toxicity of local anesthetics, we have found that moderate hyperkalemia greatly increases the ventricular slowing effect of bupivacaine and lidocaine in the isolated perfused rat heart.[5] No data of this nature exists for the intact, innervated heart. In the present study we have examined, in lightly anesthetized and mechanically ventilated dogs, the effects of hyperkalemia on the central nervous system (CNS) and cardiovascular toxicity of lidocaine and bupivacaine.

Materials and Methods

Twenty-eight mongrel dogs of either sex (average weight of 15.4 kg) were divided into two equal groups—those receiving bupivacaine and those receiving lidocaine. A further subdivision of each group was made placing seven dogs each in either a normokalemic or hyperkalemic subgroup.

The anesthetic management of all subgroups was the same: animals were sedated with morphine sulfate 1–2 mg/kg intravenously, and endotracheal intubation was performed following injection of succinylcholine (4 mg). Anesthesia was maintained with morphine sulfate (average total dose 2.9 ± 0.9 mg/kg), 60% nitrous oxide and oxygen. Muscle paralysis was maintained with pancuronium given in 2.0 mg doses as necessary, and ventilation was adjusted to maintain normal arterial blood P_{CO_2} and *p*H. Arterial P_{O_2} was greater than 100 mmHg in all cases. Normothermia was maintained throughout the experiment.

Right atrial and Swan–Ganz® (American Edwards Laboratories, Santa Ana, California) catheters were introduced via the right external jugular vein, and cannulation of the femoral artery was performed. Following a left thoracotomy at the level of the fourth intercostal space, a left ventricular catheter was placed via the left auricle and an electromagnetic flow probe was placed around the ascending aorta.

The right atrial catheter was used for the introduction of the thermal indicator (0.5° C saline) into the atrium. Cardiac output was measured with the Swan–Ganz® catheter and a Waters C-100® (Waters Instruments, Inc., Rochester, Minnesota) thermal dilution cardiac output computer. In a small number of animals cardiac output was obtained from the electromagnetic flow probe, which was calibrated by a gravity flow method. With the probe in place around the aorta, zero flow was taken to occur during diastole, just prior to the ejection stroke. Lead II ECG, femoral arterial blood pressure, left ventricular end-diastolic pressure, and EEG were monitored continuously and recorded at appropriate intervals. EEG surface leads

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were F_{pl} and O_l with A_l as common. Total peripheral resistance was derived as standard peripheral resistance units.

Animals received intravenous infusions of either bupivacaine or lidocaine at arbitrarily chosen rates of 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ and 3 $mg\ kg^{-1} \cdot min^{-1}$, respectively. Normokalemia was defined as the average initial serum potassium concentration for all the dogs studied (2.7 ± 0.05 SEM mEq/l). The serum potassium concentration was increased in animals within the hyperkalemic subgroups by intravenous administration of potassium chloride at the rate of 0.5 $mEq \cdot kg^{-1} \cdot h^{-1}$ until a plateau at approximately twice the normal value (mean 5.4 ± 0.05 SEM) was reached. This plateau was maintained during the infusion of the local anesthetic. The bupivacaine and lidocaine infusions were continued beyond the appearance of central nervous system toxicity and terminated when cardiovascular toxicity occurred. Central nervous system toxicity was defined as seizure activity (spikes of high frequency and voltage) on the EEG. Cardiovascular toxicity was defined arbitrarily as a mean arterial blood pressure of approximately 40 mmHg.

Statistical comparisons of the data were made in the following manner: between normokalemia and hyperkalemia or between bupivacaine and lidocaine an unpaired *t* test was used. Within any of those groups comparisons were made with a paired *t* test. A one-way analysis of variance was used to compare data from the four groups. Cardiovascular to seizure toxicity ratios were determined by averaging the individual ratios within each group.

Results

Bupivacaine (Table 1)

With the onset of seizure activity on the EEG, mean blood pressure, left ventricular end-diastolic pressure, and total peripheral resistance were increased significantly from control. Significant increases also were seen in the P-R interval of the normokalemic subgroup and in the P-R and Q-T intervals and the QRS duration of the hyperkalemic subgroup. As the infusion was continued beyond seizure, QRS complexes widened farther, and ventricular eptopic beats and ventricular tachycardia usually occurred. At the end point for cardiovascular toxicity, hemodynamic changes that were significant ($P < 0.05$) from control were a decrease in mean arterial pressure and cardiac output and an increase in left ventricular end-diastolic pressure and heart rate.

In the normokalemic dogs the seizure dose of bupivacaine was (mean ± SEM) 5.1 ± .38 mg/kg, whereas the cardiotoxic dose was 21.1 ± 3.38 mg/kg (fig. 1). The cardiovascular to seizure dose toxicity ratio was 4.2 ± 0.59 (fig. 2). For hyperkalemia the seizure dose of bupivacaine was 6.5 ± 0.7 mg/kg, whereas the cardiotoxic dose was 10.6 ± 2.0 mg/kg (fig. 1). The cardiovascular to seizure dose toxicity ratio in this case was 1.6 ± 0.31 (fig. 2). Note that while the cardiotoxic dose and the cardiovascular to seizure dose toxicity ratios for normokalemia and hyperkalemia were significantly different from one another, the seizure doses were not.

Table 1. The Influence of Hyperkalemia on Measured and Derived Parameters at the Two Levels of Bupivacaine Intoxication

	Control	Seizure	Cardiotoxicity
Normokalemic			
MAP(mmHg)	100 ± 11	157 ± 27*	41 ± 31*
LVEDP(mmHg)	5.7 ± 3.4	13.7 ± 6.6*	10.5 ± 4.6*
CO(l/min)	1.8 ± 0.5	1.9 ± 0.9	0.6 ± 0.2*
TPR(PRU)	3.3 ± 0.7	5.7 ± 2.2*	2.5 ± 2.5
HR(beats/min)	120 ± 22	142 ± 34	127 ± 40
P-R(s)	0.09 ± 0.01	0.11 ± 0.01*	
QRS(s)	0.07 ± 0.01	0.08 ± 0.02	
Q-T(s)	0.22 ± 0.02	0.21 ± 0.03	
Hyperkalemic			
MAP(mmHg)	120 ± 11	166 ± 17*	47 ± 18*
LVEDP(mmHg)	3.0 ± 3.0	10.0 ± 7.8*	11.7 ± 7.5*
CO(l/min)	2.1 ± 0.7	1.9 ± 1.0	0.5 ± 0.2*
TPR(PRU)	3.9 ± 2.0	6.5 ± 3.1*	5.6 ± 4.1
HR(beats/min)	146 ± 19	151 ± 24	181 ± 63*
P-R(s)	0.08 ± 0.01	0.12 ± 0.01*	
QRS(s)	0.07 ± 0.01	0.11 ± 0.03*	
Q-T(s)	0.19 ± 0.02	0.21 ± 0.03*	

Values expressed as mean ± SD.
Mean arterial pressure = MAP; cardiac output = CO; left ventricular end-diastolic pressure = LVEDP; total peripheral resistance = TPR; heart rate = HR; ECG intervals P-R, Q-T, and QRS duration.
* $P < 0.05$ comparisons made with control.

Lidocaine (Table 2)

At the seizure dose, no significant hemodynamic changes occurred in the normokalemic group. In the hyperkalemic group there were significant increases in mean arterial blood pressure and heart rate. There were no changes in the P-R or Q-T interval or in the QRS duration in either the normokalemic or the hyperkalemic groups. As the infusion was continued beyond the seizure dose, a gradual decrease in mean arterial blood pressure, cardiac output, and heart rate occurred. At the end point for cardiovascular toxicity these variables were significantly less than control. In contrast to bupivacaine, the arrhythmias encountered with lidocaine at the cardiotoxic end point were usually nodal or idioventricular rhythms with an average rate of approximately 100 beats/min.

In the normokalemic dogs the seizure dose of lidocaine was 25.8 ± 4.3 mg/kg, whereas the cardiotoxic dose was 96.6 ± 14.2 mg/kg (fig. 1). The cardiovascular to seizure dose toxicity ratio was 4.8 ± 1.32 (fig. 2). For hyperkalemia the seizure dose of lidocaine was 24.9 ± 3.7 mg/

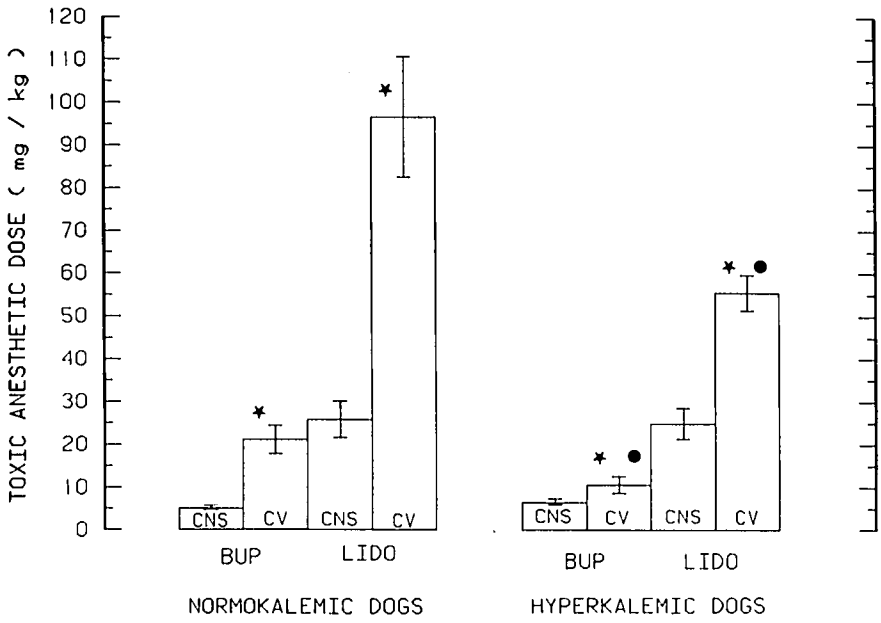

FIG. 1. Toxic dose of bupivacaine (BUP) and lidocaine (LIDO) under conditions of normokalemia and hyperkalemia. Seizure dose (CNS) and cardiotoxic dose (CV). Mean ±1 SEM. ★ $P < 0.05$ when compared with precursory seizure dose. ● $P < 0.05$ when compared with corresponding normokalemic cardiotoxic dose.

kg, whereas the cardiotoxic dose was 55.5 ± 4.2 mg/kg (fig. 1). The cardiovascular to seizure dose toxicity ratio in this case was 2.4 ± 0.26 (fig. 2). Note, again, that hyperkalemia did not affect the seizure dose, while it significantly did lower the dose of lidocaine needed for cardiotoxicity. In this study, however, the lidocaine cardiovascular to seizure dose toxicity ratios for normokalemia and hyperkalemia were not statistically different from one another.

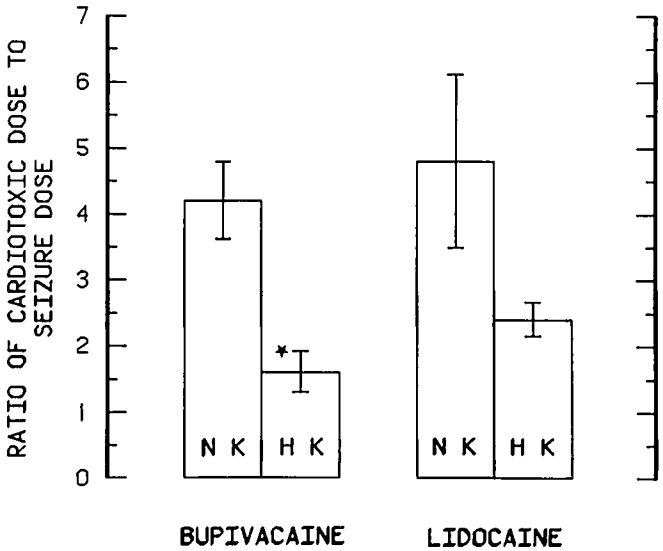

FIG. 2. Ratios of cardiotoxic to seizure doses of bupivacaine and lidocaine under conditions of normokalemia (NK) and hyperkalemia (HK). Mean values of individual ratios ±1 SEM. ★ $P < 0.05$ when compared with normokalemic ratio.

Discussion

In these experiments adequately ventilated dogs anesthetized with morphine–N_2O and paralyzed with pancuronium developed EEG seizure activity following cumulative intravenous doses of 5.1 mg/kg of bupivacaine or 25.8 mg/kg of lidocaine. These doses of local anesthetic are similar to the cumulative intravenous doses found by Liu and associates[6] to cause clinical convulsive activity in unanesthetized dogs (bupivacaine, 5.0 mg/kg; lidocaine, 22.0 mg/kg) and, also, to the cumulative intravenous doses found by deJong *et al.*[3] to induce EEG seizure activity in gallamine-paralyzed cats (bupivacaine, 5.3 mg/kg; lidocaine 22.0 mg/kg). The reports by Liu and deJong are comparable to ours in that both expressed dose as the cumulative amount of drug administered either by continuous intravenous infusion (deJong) or by incremental intravenous injection (Liu). However, they differ from ours as to the rates of drug administration. We administered bupivacaine at 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ and lidocaine at 3.0 $mg \cdot kg^{-1} \cdot min^{-1}$. deJong administered bupivacaine at 1.0 $mg \cdot kg^{-1} \cdot min^{-1}$ and lidocaine at four times that rate. Liu used equal incremental injections for both drugs. Despite these differing rates and methods of administration, the cumulative threshold doses for seizure activity are almost identical for bupivacaine in all three studies. Our cumulative dose for lidocaine is 17% higher than that reported by either of the other groups. Malagodi *et al.*[7] found that increasing the rate of drug infusion decreased the convulsive dose of etidocaine but not that of bupivacaine. Both nitrous oxide and muscle relaxants have been reported to increase the local anesthetic seizure threshold. deJong *et al.*[8] have found that 70% N_2O in-

creases the intravenous convulsant dose of lidocaine in cats by approximately 50%. Munson and Wagman[9] report that gallamine increases the seizure dose for lidocaine in monkeys by 42%. In other experiments deJong and associates[10] report no difference between gallamine and metocurine (in cats) as regards effect on seizure threshold for bupivacaine. To our knowledge no comparative data for pancuronium are available. Our use of nitrous oxide and pancuronium may have contributed to our finding of a higher seizure dose for lidocaine than that reported by either deJong or Liu and their collaborators. We do not know why our seizure dose of bupivacaine also was not increased.

The normokalemic animals in our study that received seizure doses of lidocaine did not develop significant changes in any of the measured or calculated hemodynamic variables. On the other hand, those normokalemic animals that received convulsive doses of bupivacaine exhibited significant increases in mean arterial pressure (+57%), left ventricular end-diastolic pressure (+140%), and total peripheral resistance (+73%). deJong *et al.*[3] also observed increases in blood pressure following injection of convulsive doses of bupivacaine but not of lidocaine. We did not observe ECG changes during the infusion of seizure doses of lidocaine. During bupivacaine infusion, the P-R interval significantly was increased and, with the combination of hyperkalemia and the seizure dose of bupivacaine, we found significant increases in both the P-R and QT intervals and in the duration of the QRS complex. deJong[3] observed widening of the QRS with bupivacaine but not with lidocaine.

Cardiovascular toxicity, defined by us as a mean arterial pressure of approximately 40 mmHg, was encountered during normokalemia only when more than four times the seizure dose of either local anesthetic was administered. We found that the hypotension encountered at the cardiovascular toxic dose was due primarily to depression of myocardial pump function. Total peripheral resistance was not different from control for either lidocaine or bupivacaine while cardiac output markedly and significantly was decreased by both drugs. Left ventricular end-diastolic pressure significantly was increased by bupivacaine. Myocardial depression also was observed by Liu and associates[11] to be the primary factor responsible for the hypotension induced by bupivacaine and lidocaine. These investigators observed, as we did, only minimal changes in total peripheral resistance. For both lidocaine and bupivacaine, they described the development of sinus bradycardia and, ultimately, mechanical asystole with persistance of electrical cardiac activity. We observed different rhythm changes. For bupivacaine, ventricular tachycardia was the most frequent rhythm encountered, while for lidocaine the rhythm was nodal or idioventricular with an average ventricular rate of about 100 beats/min. We speculate that the difference between Liu *et al.* and our observations as regards rate and rhythm changes may have been due, at least in part, to the fact that they carried out their experiments in pentobarbital-anesthetized dogs, while we used dogs that were anesthetized with morphine and nitrous oxide.

TABLE 2. The Influence of Hyperkalemia on Measured and Derived Parameters at the Two Levels of Lidocaine Intoxication

	Control	Seizure	Cardiotoxicity
Normokalemic			
MAP(mmHg)	100 ± 18	119 ± 38	29 ± 16*
LVEDP(mmHg)	9.3 ± 3.7	15.0 ± 5.0	14.0 ± 6.5
CO(l/min)	2.1 ± 0.7	1.7 ± 0.6	0.8 ± 0.3*
TPR(PRU)	2.2 ± 0.7	2.9 ± 0.9	1.8 ± 0.7
HR(beats/min)	123 ± 17	155 ± 38	98 ± 27*
P-R(s)	0.10 ± 0.02	0.09 ± 0.02	
QRS(s)	0.07 ± 0.01	0.07 ± 0.01	
Q-T(s)	0.20 ± 0.05	0.21 ± 0.02	
Hyperkalemic			
MAP(mmHg)	123 ± 18	151 ± 21*	32 ± 15*
LVEDP(mmHg)	10.8 ± 6.4	15.0 ± 9.8	10.0 ± 7.0
CO(l/min)	1.8 ± 0.5	1.9 ± 0.6	0.6 ± 0.4*
TPR(PRU)	4.2 ± 1.7	5.0 ± 2.0	3.8 ± 2.5
HR(beats/min)	122 ± 28	183 ± 25*	109 ± 66
P-R(s)	0.09 ± 0.02	0.09 ± 0.02	
QRS(s)	0.07 ± 0.01	0.07 ± 0.01	
Q-T(s)	0.19 ± 0.04	0.17 ± 0.02	

Values expressed as mean ± SD.
Mean arterial pressure = MAP; cardiac output = CO; left ventricular end-diastolic pressure = LVEDP; total peripheral resistance = TPR; heart rate = HR; ECG intervals P-R, Q-T and QRS duration.
* $P < 0.05$ comparisons made with control.

In the present study hyperkalemia did not alter the seizure dose of either lidocaine or bupivacaine. While the seizure dose of bupivacaine did cause increased lengthening of the P-R and Q-T intervals and increased duration of the QRS complex in the presence of hyperkalemia, no such effect was noted for lidocaine. We observed no effect of hyperkalemia on the type or incidence of arrhythmias for either lidocaine or bupivacaine. The major finding of this study is that the changes in cardiac rhythm, depression of cardiac output, and severe hypotension were brought about by significantly smaller (approximately one-half) doses of both bupivacaine and lidocaine in the presence of moderate hyperkalemia. Hyperkalemia decreased the cardiovascular to seizure toxicity ratio significantly for bupivacaine but not for lidocaine. Hyperkalemia has been demonstrated to enhance the depressant effect of local anesthetics on conduction parameters in the heart.[12–14] Whether this relationship plays a role in producing the hemodynamic changes observed here is not known. Local anesthetics directly depress myocardial contractility.[15,16] Our data suggest that this effect may be enhanced by hyperkalemia. However, there is a need for other studies in which changes in force of myocardial contraction are examined

in the absence of changes in other variables such as heart rate, preload, or afterload, to determine whether such enhancement truly exists.

We do not know if hyperkalemic enhancement of local anesthetic cardiotoxicity occurs in humans. A recent clinical report[17] describes the occurrence of bradycardia and hypotension following the administration of bupivacaine for an axillary block in a patient who was hyperkalemic and acidotic. This patient had other similar blocks in the absence of hyperkalemia or acidosis without incident, but inasmuch as data concerning drug absorption are not given, it is not clear to what extent hyperkalemia or acidosis contributed to this patient's problem. Hyperkalemic enhancement of local anesthetic cardiotoxicity has been reported in several mammalian species.[5,12–14] It therefore may be prudent to exercise care in the use of local anesthetics in patients who are hyperkalemic.

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