Anesthesiology
65:61–66, 1986

Amide Local Anesthetic Alterations of Effective Refractory Period Temporal Dispersion: Relationship to Ventricular Arrhythmias

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The hemodynamic and electrophysiologic effects of bupivacaine, etidocaine, mepivacaine, and lidocaine were investigated in 32 pentobarbital-anesthetized adult mongrel dogs. Following equipotent dosing, all four agents produced similar hemodynamic effects: decrease in stroke volume and cardiac output, heart rate slowing, increase in systemic vascular resistance, and increases in pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP). The effects of the various agents on the ECG were different. Compared with the control period, mepivacaine and lidocaine produced slight increases and etidocaine and bupivacaine much greater increases in: 1) the area under the curve of the T-wave; 2) lengthening of the QTU interval; and 3) enhancement of the "slow wave" or U-wave following the T-wave. The effects of the various agents on effective refractory period (ERP) temporal dispersion were dramatically different. The ERP temporal dispersion increased to 48.3 ± 36.0 ms following mepivacaine, 37.4 ± 10.1 ms following lidocaine, 97.1 ± 36.2 ms following bupivacaine, and 92.5 ± 30.5 ms following etidocaine. Six of seven bupivacaine, six of seven etidocaine, two of eight mepivacaine, and none of eight lidocaine animals sustained a polymorphic, undulating ventricular tachycardia similar to Torsades de Pointes following burst ventricular pacing. The results of this study suggest that bupivacaine, etidocaine, and occasionally mepivacaine can result in a Torsades de Pointes-like syndrome following intravenous administration. The magnitude of ERP temporal dispersion differences between the various agents appears to explain their differential arrthymogenicity. (Key words: Anesthetics, local: bupivacaine, etidocaine, lidocaine, mepivacaine. Complications: arrhythmia. Heart: arrhythmia; cardiac output; conduction. Pharmacology: local anesthetic.)

FOUR AMIDE LOCAL anesthetics, bupivacaine, etidocaine, mepivacaine, and lidocaine, are widely used in anesthesiology today. However, there is evidence that they differ markedly in their effects on the heart when administered intravenously by accident. Lidocaine and mepivacaine are unlikely to cause serious ventricular arrhythmias when administered intravenously,[1–3] whereas both bupivacaine and etidocaine have been implicated in causing serious ventricular arrhythmias following intravenous administration.[1,3–5] We recently reported that toxic serum concentrations of bupivacaine lengthen the QTU interval and appear to result in a Torsades de Pointes-like rhythm abnormality.[6]

The mechanism of the unusual ventricular arrhythmias from excessive levels of bupivacaine and etidocaine is currently not well defined. Increases in QTU interval duration and area under the curve of the T-wave have been reported to result in effective refractory period (ERP) temporal dispersion.[7,8] The magnitude of ERP temporal dispersion is related to ventricular arrhythmias.[9] Thus, comparison of cardiac electrophysiologic effects, especially ERP temporal dispersion, of bupivacaine and etidocaine with mepivacaine and lidocaine may allow for greater understanding of local anesthetic cardiovascular toxicity. This study evaluated hemodynamic and electrophysiologic cardiovascular effects, including ERP temporal dispersion, of bupivacaine, etidocaine, mepivacaine, and lidocaine in an attempt to explain the apparent differential cardiovascular toxicity and arrhythmogenicity of these agents.

Methods

Thirty-two adult mongrel dogs weighing 22.1 ± 2.5 kg each were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, and immobilized with pancuronium bromide, 0.15 mg/kg. A cuffed endotracheal tube was inserted and the animals were ventilated with 100% oxygen using an Airshields™ ventilator. Tidal volume, respiratory rate, and sodium bicarbonate administration (0.5–1.0 mEq/kg 30 min prior to the experimental period) were adjusted to provide the following arterial blood gas values: *p*Ha 7.35–7.45, Pa_{CO_2} 32–40 mmHg, and Pa_{O_2} 300–500 mmHg. Arterial blood gases were also measured following administration of the local anesthetic agent.

A catheter was placed in the left femoral artery for arterial blood gas analysis, direct recording of the arterial pressure, and local anesthetic serum concentration sampling. Using the right femoral vein, a Swan Ganz catheter (American Edwards® model 93-131-7F) was placed into the pulmonary artery. Cardiac output was determined and reported as an average of five readings using the

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Received from the University of Kentucky Medical Center. Accepted for publication February 19, 1986. Supported by a Winthrop Breon Laboratories Grant and the University of Kentucky PSP Research Starter Grant.

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TABLE 1. Dose Schedule For Local Anesthetic Bolus and Infusion

Drug	Bolus (mg/kg)	Infusion Rate ($mg \cdot kg^{-1} \cdot min^{-1}$)	Estimated Serum Level ($\mu g/ml$)
Bupivacaine	4	0.2	7.0
Etidocaine	8	0.3	9.0
Mepivacaine	16	0.4	15.0
Lidocaine	16	0.4	15.0

thermodilution technique and a computer (American Edwards® model 9520A cardiac output computer). Lead II surface ECG, arterial blood pressure, right atrial pressure, and pulmonary artery pressure were recorded continuously on a polygraph (Grass® model 7A).

A sternotomy and pericardiotomy were performed to expose the epicardial surface of the heart following an additional 10 mg/kg of pentobarbital intravenously. Two unipolar plunge needle electrodes were placed one cm apart in the left ventricular apex to allow for ventricular pacing. To determine the ERP, ten unipolar plunge needle electrodes (Ethicon® multifilament steel, polyethylene-coated, temporary cardiac pacing wires) were randomly placed in the left ventricle epicardium and left in the exact same position throughout the entire experimental period. The reference electrode for the ten ERP electrodes was placed in the chest wall. The ERP at each of the 10 epicardial electrode sites was determined with a programmable stimulator (Medtronics® model 5325) using a rectangular stimulus of 1.8 ms at twice diastolic threshold. Eight successive sinus rhythm depolarizations (S_1) were scanned and following the eighth beat, a cathodal premature stimulus (S_2) was delivered at progressively shorter intervals until the testing premature stimulus failed to elicit a propagated response. The ERP was defined as the longest interval between the preceding R-wave and the premature stimulus that failed to elicit a propagated response. ERP temporal dispersion was defined as the difference between the longest and shortest value of the ten measured ERPs. During the sensing period of eight regular sinus beats (S_1) the sequence was repeated if any premature atrial or ventricular depolarizations occurred. Each time the ERP was determined at each site, the method was repeated to insure that the two measured values were within 5 ms of each other. This procedure was then repeated at all ten electrode sites.

The experimental protocol was as follows: during a 30-min control period, the hemodynamic parameters of mean arterial pressure (MAP), pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) were obtained. The lead II was recorded at 100 mm/s chart-paper speed and PR, RR, QRS, and QTU intervals measured. The area under the curve of the T-wave was determined following enlargement of the ECG tracing, and the T-wave was carefully cut out and weighed. Following collection of data in the control period, the animal was administered a randomized local anesthetic to provide for steady-state serum levels at the dose schedule shown in table 1. Each animal received only one local anesthetic.

Thirty minutes following the bolus and infusion administration of the local anesthetic, the hemodynamic and electrophysiologic parameters were repeated. The ERP was determined at the ten left ventricular sites. An arterial serum sample was obtained for local anesthetic serum assay at the time of electrophysiologic measurement. Prior investigations with bupivacaine[6] and preliminary work with the other local anesthetics in our laboratory by frequent serum concentration sampling revealed that steady-state conditions exist at the time of hemodynamic and electrophysiologic measurement. The method of analysis for local anesthetics has been previously described in detail[10] and uses mepivacaine as the internal standard. For the mepivacaine assay, bupivacaine was used as the internal standard.

The ventricular tachycardia threshold measurement method has been previously reported,[6] and uses a programmable stimulator (Medtronics® model 5325). Using a rectangular stimulus of 1.8 ms at twice diastolic threshold, 10-s burst ventricular pacing was done beginning with a rate of 200 beats/min. The rate was increased by 50 beats/min every min until either ventricular tachycardia was induced or a rate of 400 beats/min had been reached. Rates of greater than 400 beats/min were not attempted. One minute was allowed to elapse between each period of ventricular stimulation to allow for correction of hypotension from the tachycardia and washout of myocardial metabolites.

The animals were resuscitated following induction of sustained ventricular arrhythmias with a fixed-dose combination of bretylium, 15 mg/kg iv, epinephrine, 40 μg/kg iv, and bicarbonate, 1 mEq/kg iv. This regimen was used based on results of earlier investigations demonstrating effectiveness of epinephrine and bretylium.[6,11] Direct-current (DC) cardioversion was used when necessary.

Data analysis was done with Student's t test for paired data for comparison of hemodynamic and electrophysiologic effects before and after local anesthetic treatment. Analysis of variance along with Student's t test for unpaired data was used for between-group comparison of hemodynamic and electrophysiologic results. Chi-square test was used for between-group comparison of animals experiencing ventricular arrhythmias. A probability level of $P < 0.05$ was considered statistically significant.

Results

Serum levels at the time of electrophysiologic measurement of the local anesthetics were: 15.4 ± 3.8 μg/

ml for lidocaine, 13.9 ± 2.8 μg/ml for mepivacaine, 7.3 ± 2.6 μg/ml for bupivacaine, and 8.7 ± 2.8 μg/ml for etidocaine. The overall hemodynamic effects of all amide local anesthetics studied were similar to that previously reported.[6,12] Compared with the control period, all agents produced a decrease in cardiac output and stroke volume of approximately 40–50% and a moderate 10–20% slowing of heart rate with a reflex increase in systemic vascular resistance. MAP was altered in a nonsignificant fashion. Small, statistically significant increases in PAP and PCWP pressures were found with all agents.

Following administration of the local anesthetic, one animal in the etidocaine group and one animal in the bupivacaine group sustained spontaneous ventricular tachycardia. No spontaneous ventricular arrhythmias occurred in any other animal following administration of the local anesthetic agent. In spite of the similar hemodynamic effects of the different agents, the effect on the surface ECG differed (fig. 1). Compared with the control period, mepivacaine and lidocaine produced small statistically, significant increases in: 1) the area under the curve of the T-wave; 2) lengthening of the QTU interval; and 3) enhancement of the "slow wave" or inverted U-wave following the T-wave (table 2). In contrast, bupivacaine and etidocaine produced much greater alterations in these parameters (table 2).

The effects of the four local anesthetics on ERP temporal dispersion are shown in table 3. All four agents produced an increase in the ERP and ERP temporal dispersion. In two mepivacaine animals, a large increase of ERP temporal dispersion from 20 ms in the control period to greater than 80 ms following drug administration occurred. The ERP alterations produced by bupivacaine and etidocaine differed from lidocaine in that the alteration produced was not always an increase in ERP at each site (table 4). Lidocaine almost always produced a consistent increase in the ERP at each site, while bupivacaine and etidocaine produced an increase in most sites, but some areas experienced a decrease in ERP from the control period. For example, in one animal, at sites four and seven the ERP decreased from 182 to 150 ms and 173 to 163 ms following bupivacaine administration (table 4).

The two animals that sustained spontaneous ventricular tachycardia following etidocaine and bupivacaine administration were omitted from further analysis. With the exception of the one etidocaine animal sustaining a spontaneous, monomorphic ventricular tachycardia, all animals that sustained ventricular tachycardia following local anesthetic administration experienced an unusual polymorphic, undulating ventricular tachycardia. Burst ventricular pacing resulted in six of seven animals in the etidocaine group and six of seven animals in bupivacaine group sustaining a polymorphic, undulating ventricular tachycardia similar to that previously reported.[6] No animals in the lidocaine group sustained ventricular tachycardia and two of eight animals in the mepivacaine group sustained ventricular tachycardia. Compared with the other mepivacaine animals, the two animals that sustained ventricular tachycardia had a much greater increase in area under the curve of the T-wave and increase in the QTU interval (fig. 2), along with a much greater increase

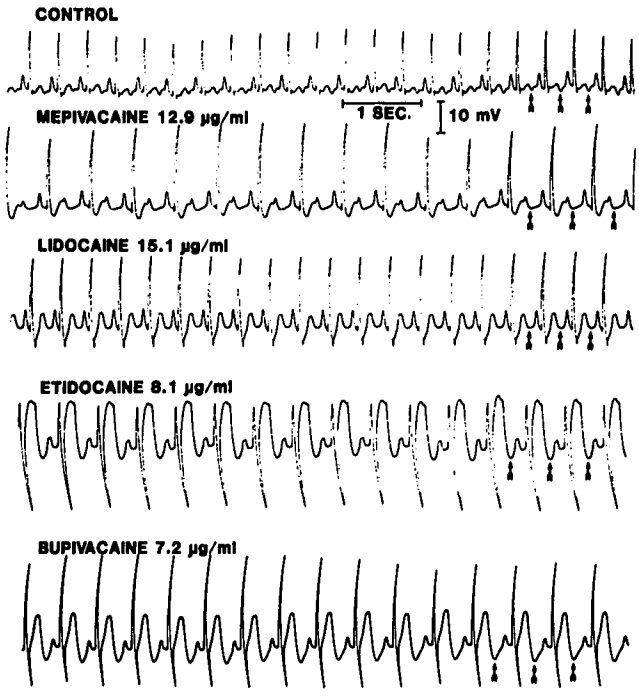

FIG. 1. Lead II surface ECG alterations produced in animals administered lidocaine, mepivacaine, etidocaine, and bupivacaine along with a representative control period. Compared with each animal's control period ECG, the area under the curve of the T-wave was increased by 200% for mepivacaine, 190% for lidocaine, 765% for etidocaine, and 545% for bupivacaine. The increase in the QTU interval compared with the control period was 20% for mepivacaine, 15% for lidocaine, 74% for etidocaine, and 65% for bupivacaine. The arrows point to the enhancement of the inverted U, or "slow wave," following the T-wave produced by etidocaine and bupivacaine. Lidocaine and mepivacaine produced only a minor enhancement of this "slow wave."

TABLE 2. Alterations in T Wave Area Under the Curve and QTU Interval

Drug	n	T Wave Area Under the Curve Increase*	QTU Interval Duration Increase*
Mepivacaine	8	375 ± 350†	30 ± 18†
Lidocaine	8	200 ± 75†	10 ± 5†
Bupivacaine	7	[illegible]0 ± 260†‡	60 ± 25†‡
Etidocaine	7	[illegible]0 ± 290†‡	55 ± 30†‡

All values reported as mean [illegible].
* Per cent increase from control.
† $P < 0.05$ from control.
‡ $P < 0.05$ compared with lidocaine group.

TABLE 3. Effective Refractory Period (ERP) Results

Drug	n	Control	Drug ERP	Control Dispersion	Drug Dispersion
Mepivacaine	8	197 ± 7.9	232 ± 35.9*	23.6 ± 7.1	48.3 ± 36.0*
Lidocaine	8	183 ± 8.8	216 ± 19.1*	23.6 ± 8.1	37.4 ± 10.1*
Bupivacaine	7	179 ± 10.1	235 ± 59.1*	18.7 ± 4.6	97.1 ± 36.2*†
Etidocaine	7	186 ± 11.1	256 ± 58.7*	22.0 ± 4.4	92.5 ± 30.5*†

All values in ms and reported as mean ± SD.
* $P < 0.05$ from control.
† $P < 0.05$ compared with lidocaine group.

of ERP temporal dispersion. When all animals in the four local anesthetic groups were pooled and compared with the animals that sustained ventricular tachycardia *versus* those that did not, a significant difference was found between the two groups in the T-wave area under the curve and ERP temporal dispersion (table 5), although some overlap did occur. All bupivacaine and mepivacaine animals and all but one etidocaine animal were successfully resuscitated with the use of epinephrine, bretylium, and bicarbonate and DC cardioversion.

Discussion

This study compared equipotent doses of four amide local anesthetics, bupivacaine, etidocaine, mepivacaine, and lidocaine, which are commonly used in modern anesthesia practice. The bolus doses chosen were calculated based on nerve block and LD_{50} potency ratios between the four drugs. Bupivacaine has been reported to be approximately twice as potent as etidocaine and four times as potent as lidocaine and mepivacaine.[12] The constant infusion rate for each drug was selected based on drug clearance rates. Bupivacaine clearance in dogs during constant infusion has been reported to be approximately twice that of lidocaine.[13] It was assumed that mepivacaine clearance would be similar to lidocaine, while etidocaine clearance would be between bupivacaine and lidocaine. During the steady-state conditions of this study, all agents produced similar cardiac hemodynamic alterations. Thus, the dosing regimen appeared to provide for equivalent hemodynamic conditions between all four agents. Pentobarbital and pancuronium bromide have indirect cardiac effects through the sympathetic nervous system.[14,15] Therefore, during pentobarbital anesthesia with pancuronium immobilization, there will be a relative increase in sympathetic nervous tone. Thus, the effects of the anesthetic may have contributed to the similar stable hemodynamic conditions following administration of the four different local anesthetic agents.

TABLE 4. Effective Refractory Period (ERP) Dispersion Changes Produced by Lidocaine and Bupivacaine in Two Representative Animals

	Control	Lidocaine Administration	Control	Bupivacaine Administration
ERP Measurement Site				
1	184	235	178	235
2	172	213	176	230
3	175	245	178	244
4	193	251	182	150
5	172	238	180	220
6	180	246	180	230
7	182	238	173	163
8	178	213	184	220
9	180	235	168	266
10	174	235	185	230
ERP Temporal Dispersion	21	38	16	116

All values in ms.

Despite similar hemodynamic alterations, the ECG effects were variable (fig. 1). All lidocaine and most mepivacaine animals sustained mild increases, while bupivacaine, etidocaine, and two mepivacaine animals sustained marked increases in: 1) the area under the curve of the T-wave; 2) lengthening of the QTU interval and; 3) enhancement of the inverted U-wave or "slow wave" following the T-wave.

All four drugs produced increases in the absolute mean ERP. The ERP temporal dispersion was increased by all four local anesthetics, but clear differences were present between lidocaine *versus* etidocaine and bupivacaine. Most mepivacaine animals had ERP temporal dispersion similar to lidocaine (30–40 ms), but two animals sustained much greater increases in dispersion (80–100 ms). The ERP temporal dispersion consisted of more than unequal lengthening of the ERP, because many animals, particularly following etidocaine and bupivacaine, sustained a decrease in the measured ERP at certain sites (table 4). If only a direct cardiac depressant effect from the local anesthetic were involved with the ERP temporal dispersion, then it would be likely that the ERP would always increase at each site, particularly because heart rate always decreased. However, because it was found that following the drug administration at some measurement sites the ERP decreased, then it is possible that other systemic toxic effects such as CNS stimulation could be involved. It has been reported that CNS stimulation or stellate ganglion sympathetic imbalance can cause T-wave alterations and increased ERP temporal dispersion, much like that ob-

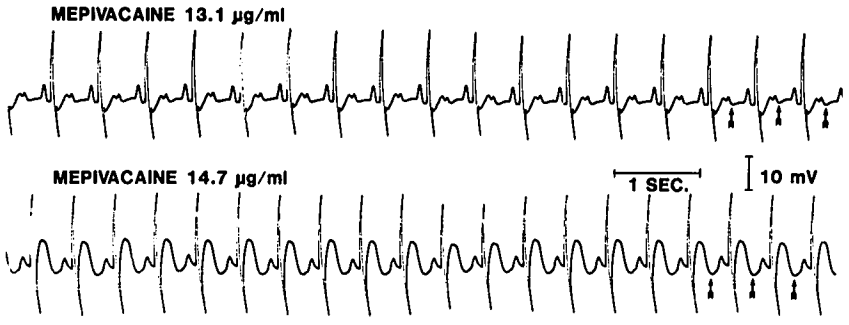

FIG. 2. Comparison of lead II surface ECG alterations in two mepivacaine-treated animals. When compared with the control period, the first tracing reveals an 18% increase in the QTU interval, a 125% increase in T-wave area under the curve, and a minor enhancement of the "slow wave" following the T-wave. The effective refractory period (ERP) temporal dispersion was 38 ms. This animal did not sustain ventricular tachycardia upon ventricular pacing. The second tracing reveals an animal with a 515% increase in area under the curve of the T-wave, a 65% increase in the QTU interval, and a greatly enhanced "slow wave" following the T-wave. The ERP temporal dispersion was 93 ms. This animal sustained a polymorphic, undulating ventricular tachycardia following ventricular pacing.

served in this study.[16,17] CNS sympathetic stimulation appears to be a factor in the genesis of bupivacaine ventricular arrhythmias.[18] It is possible, therefore, that CNS stimulation, along with direct cardiac conduction depression from the potent local anesthetics, may contribute to reentrant ventricular arrhythmias.

Prior investigations have demonstrated that abnormal lengthening of the QTU interval and increased area under the curve of the T-wave are related to increased ERP temporal dispersion.[7,8] Normally the ERP is consistent when measured at different sites throughout the left ventricle. Various conditions, such as ischemia, drugs, or electrolyte disturbances, can result in nonuniform changes in the ERP.[19] The magnitude of ERP temporal dispersion has been shown to be related to the threshold of ventricular arrhythmias.[9] All local anesthetics tested in this study increased the ERP temporal dispersion, but ventricular arrhythmias usually occurred only following the largest increases. Thus, it appears that a margin of safety is present with regard to ERP temporal dispersion. Increases of ERP temporal dispersion of 100% above control are well tolerated, but increases greater than 200–300% above control lead to ventricular arrhythmias. Bupivacaine and etidocaine are most likely to increase ERP temporal dispersion above this critical value.

Reentrant ventricular arrhythmias such as ventricular tachycardia are most likely to occur during the conditions of slow intracardiac conduction and early repolarization. Bupivacaine and etidocaine have been documented to cause slow intracardiac conduction.[20],† The ERP nonuniformity produced by these agents results in some areas of the ventricle having a shorter ERP than others and, when combined with slow conduction, creates conditions likely to cause reentrant ventricular arrhythmias. During these conditions, if a premature depolarization should initiate in an area of slow conduction and early repolarization, ventricular tachycardia could result. This hypothesis may explain the mechanism of ventricular arrhythmia generation from amide local anesthetics.

We recently reported that toxic concentrations of bupivacaine can result in a Torsades de Pointes-like ventricular arrhythmia.[6] Results of this investigation suggest that etidocaine and, more rarely, mepivacaine can also produce this syndrome. Torsades de Pointes is a syndrome of QTU prolongation resulting in a polymorphic, undulating ventricular tachycardia. Also prominent in this syndrome is an enhanced U-wave, or "slow wave," following the T-wave.[21] It has been suggested that the ECG abnormalities are related to monophasic action potential or ERP temporal nonuniformity.[22] Ventricular arrhythmias are usually initiated by a premature ventricular depolarization occurring on the summit of the prolonged TU wave. Although a polymorphic, undulating ventricular tachycardia is most common, a monomorphic ventricular tachycardia may occur. Common causes of the syndrome include stellate ganglion imbalance; antiarrhythmic medication such as quinidine, disopyramide, or procainamide; and hypokalemia or hypomagnesemia.[21] Management of Torsades de Pointes includes methods to shorten the QTU interval and decrease ERP temporal dispersion.[23] Effective therapy includes rapid atrial pacing, isoproterenol, and bretylium.[21]

The results of this study suggest a wide cardiac safety margin for lidocaine and to a lesser extent mepivacaine,

TABLE 5. ERP Dispersion and T-wave Charges in Animals Experiencing Ventricular Tachycardia

	n	ERP Dispersion (ms)	Area Under the Curve of the T Wave*
Animals not experiencing VT	30	51.4 ± 13.1	265 ± 140
Animals experiencing VT	30	104.1 ± 26.5†	645 ± 280†

ERP = effective refractory period; VT = ventricular tachycardia.
* Per cent increase from control.
† $P < 0.05$ between groups.

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

but a narrow margin for bupivacaine and etidocaine. It appears that QT prolongation is an important parameter that can be used to explain the incidence of ventricular tachycardia following the different local anesthetics. Prior investigations lend support to these conclusions. Studying isolated rabbit heart preparations, Block and Covino found that free concentrations of drug needed for 50% QT prolongation were: 1.36 μg/ml for bupivacaine, 1.70 μg/ml for etidocaine, 11.24 μg/ml for lidocaine, and 10.34 μg/ml for mepivacaine.† The ratio of potent drugs (etidocaine and bupivacaine) to less potent drugs (lidocaine and mepivacaine) is approximately 1:7 for this specific cardiac effect. Thus, it appears the cardiac toxicity ratios of the amide local anesthetics are different than nerve block ratios (1:4 for bupivacaine:lidocaine, and 1:2 for etidocaine:lidocaine). Clarkson and Hondeghem showed that bupivacaine differs from lidocaine in its effect on cardiac sodium channels.[24] Recovery from lidocaine blockade of cardiac sodium channels is relatively rapid; however, recovery from bupivacaine blockade is quite slow. Also, the block from bupivacaine differs in that the block is rate dependent while that of lidocaine is not. These results explain the depression of cardiac conduction following bupivacaine administration and provide further evidence for the development of reentrant ventricular arrhythmias from bupivacaine.

In summary, the potent amide local anesthetics etidocaine and bupivacaine produced: 1) large increases in the QTU interval; 2) increased area under the curve of the T-wave; 3) enhanced the inverted U-wave or "slow wave" following the T-wave, and increased ERP temporal dispersion. These changes resulted in a polymorphic, undulating ventricular tachycardia similar to Torsades de Pointes following ventricular pacing. In contrast, all lidocaine animals and most mepivacaine animals only sustained mild alterations in the just-mentioned parameters and did not experience ventricular tachycardia. The results support the concept that lidocaine, and to a slightly lesser extent mepivacaine, are safer to use in clinically equivalent doses than etidocaine and bupivacaine. Future investigations should examine the mechanism of dramatic increases in ERP temporal dispersion of bupivacaine and etidocaine.

The author acknowledges the helpful secretarial assistance of Ginny Baker. Helpful technical assistance was provided in the laboratory by Winston Powell, Joan Whiteman, and medical students Ken Main and Ronald Bailiff. The author also acknowledges the helpful editorial suggestions of Richard Rice, M.D.

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