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Lidocaine, Bupivacaine, Etidocaine, and Epinephrine-induced Arrhythmias during Halothane Anesthesia in Dogs

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Arrhythmogenic doses of epinephrine were determined in six mongrel dogs anesthetized at 1.4 MAC halothane initially in the absence of local anesthetics and then at increasing arterial plasma levels of lidocaine, bupivacaine, and etidocaine. The authors gave epinephrine intravenously at 5 μg/kg/min and calculated the arrhythmogenic dose as a function of time until two or more premature ventricular contractions occurred within a 10-sec period. The control arrythmogenic dose of epinephrine was 4.66 ± 0.46 μg/kg (mean ± SEM). Arrythmogenic doses of epinephrine were increased significantly after each dose of lidocaine, bupivacaine, and etidocaine. With the largest doses studied, local anesthetic plasma levels were frequently in the toxic range. The data show that lidocaine, bupivacaine, and etidocaine equally protect against epinephrine-induced arrhythmias in dogs anesthetized with halothane. (Key words: Anesthetics, local: bupivacaine; etidocaine; lidocaine. Anesthetics, volatile: halothane. Heart: arrhythmia, antiarrhythmics; epinephrine. Potency, anesthetic: MAC. Sympathetic nervous system: catecholamines, epinephrine.)

EPINEPHRINE is frequently injected subcutaneously for hemostasis during surgical procedures. However, systemic absorption of epinephrine may induce ventricular arrhythmias, especially in the presence of halogenated inhalational anesthetics. Johnston, Eger and Wilson[1] showed that the dose of epinephrine (ED_{50}) producing ventricular arrhythmias in patients anesthetized with halothane was increased approximately 75 per cent when it was administered in lidocaine, 0.5 per cent, rather than a saline solution. This increase of arrhythmogenic threshold by lidocaine is not limited to halothane. The ventricular irritability threshold of epinephrine was nearly quadrupled in patients anesthetized with enflurane.[2] Other amide-type local anesthetics also have been shown to be antiarrhythmic, and some of them frequently are administered in combination with epinephrine for regional block procedures.[3,4] In clinical practice, inhalational agents are sometimes administered during or after injection of a local anesthetic–epinephrine mixture. Since the interactions of these local anesthetics with halothane and epinephrine combined were unknown, we determined the effects of lidocaine,‡ bupivacaine,§ and etidocaine‡ on epinephrine-induced arrythmias in dogs anesthetized at a constant depth with halothane.

Materials and Methods

Twenty-four experiments were performed on six fasted, unmedicated, male mongrel dogs weighing 19 ± 1 kg (mean ± SEM). Five additional studies were performed on three animals that did not survive the complete studies proposed. Anesthesia was induced with halothane in oxygen by mask and a cuffed endotracheal tube was placed without the use of other drugs. Femoral artery and forelimb venous cannulas were placed percutaneously and 5 per cent dextrose in lactated Ringer's solution, 10–15 ml/kg, was given prior to control measurements. The rate of fluid administration was 5 ml/kg/hr for the duration of the experiment. A volume-limited ventilator delivered a tidal volume of 12 ml/kg at a rate sufficient to maintain Pa_{CO_2} between 30 and 40 torr. End-tidal CO_2 was monitored continuously by a Godart capnograph and arterial blood P_{O_2}, P_{CO_2} and *p*H values were measured intermittently, including just prior to each epinephrine infusion. Arterial non-carbonic acid–base state (base excess) was calculated with the method described by Ruiz, Tucker and Kirby.[5] Any base excess less than −4 mEq/l was corrected with an appropriate amount of sodium bicarbonate. This correction was necessary in only 25 per cent of the experiments and required 8.9 ± 3.6 mEq (mean ± SD) of sodium bicarbonate. End-tidal halothane concentration was measured with a Beckman LB-2 infrared halothane analyzer. The instrument was calibrated with gas mixtures stored in cylinders; the compositions of the mixtures were analyzed by gas chromatography.[6] The electrocardiogram (lead II) recorded rate and rhythm. Phasic and mean arterial pressures, end-tidal CO_2, halothane concentrations and heart rate were continuously recorded on a Grass polygraph recorder and plasma concentrations of the local anesthetics were measured by gas chromatography.[7] Body temperature was maintained at 37 ± 0.5 C by external heating or cooling.

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TABLE 1. Arterial Plasma Concentrations (Mean ± SEM) of Lidocaine, Bupivacaine, and Etidocaine, and Arrhythmogenic Doses of Epinephrine before and after Each Local Anesthetic Administration in Six Dogs

	Dose of Local Anesthetic			
	Control	1	2	3
Lidocaine				
Bolus dose (mg/kg)		1.5	1.5	1.5
Infusion dose (μg/kg/min)		100	200	400
Plasma concentration (μg/ml)		2.28 ± 0.20	4.48 ± 0.40	9.56 ± 1.24
Epinephrine dose (μg/ml)	4.48 ± 0.41	6.27 ± 0.40*	7.02 ± 0.78*	8.58 ± 1.47*†
Bupivacaine				
Bolus dose (mg/kg)		0.38	0.38	0.38
Infusion dose (μg/kg/min)		25	50	100
Plasma concentration (μg/ml)		1.05 ± 0.17	1.56 ± 0.30	2.21 ± 0.31
Epinephrine dose (μg/ml)	4.68 ± 0.36	6.04 ± 0.57*	6.72 ± 0.38*	8.54 ± 0.88*†
Etidocaine				
Bolus dose (mg/kg)		0.38	0.38	0.38
Infusion dose (μg/kg/min)		25	50	100
Plasma concentration (μg/ml)		0.69 ± 0.10	1.24 ± 0.18	2.00 ± 0.22
Epinephrine dose (μg/ml)	4.80 ± 0.59	5.80 ± 0.48*	6.41 ± 0.35*	8.38 ± 1.01*†
Without local anesthetic				
Epinephrine dose (μg/ml)	4.16 ± 0.43	4.20 ± 0.72	5.00 ± 0.53	5.23 ± 0.84

Note: Bupivacaine and etidocaine were administered in one-fourth the potency doses relative to lidocaine. Therefore, equivalent plasma concentrations relative to lidocaine can be calculated by multiplying bupivacaine and etidocaine plasma values by a potency factor of 4.[9]

* $P < 0.05$ compared with control.

† $P < 0.05$ compared with Dose 1 and Dose 2.

Anesthesia was maintained at an end-tidal halothane concentration of 1.2 ± 0.02 per cent (mean ± SEM) for at least 30 min prior to study. With a halothane MAC of 0.87 per cent,[8] this concentration of halothane is equivalent to an anesthetic level of 1.4 MAC. Then, epinephrine¶ was administered directly into an intravenous catheter by a constant-volume infusion pump at a rate of 5.0 μg/kg/min until two or more premature ventricular contractions occurred within a 10-sec period. We had previously determined that this infusion rate usually induces arrhythmias after about 1 min. Epinephrine dosage was calculated as a function of time and expressed in μg/kg body weight, and is defined as the arrhythmogenic dose.

After we determined the arrhythmogenic dose of epinephrine, the local anesthetic to be studied was administered (Dose 1). The dosage consisted of a bolus injection followed by infusion at a constant rate for at least 15 min. A Latin-square design was used to determine the order in which the local anesthetics were administered. The bolus doses and three infusion rates of each local anesthetic tested are shown in table 1. We had previously determined that this time and dosage schedule produces steady-state lidocaine plasma concentrations within a variation of 7.1 ± 2.1 per cent for at least 15 min. Bolus and infusion doses of both bupivacaine and etidocaine were decreased to one-fourth the amounts of the lidocaine doses. The ratios of doses were based on their relative potencies as determined in unanesthetized primates.[9]

In each instance, the discontinuation of epinephrine and the administration of a local anesthetic restored cardiac rhythm to a normal sinus pattern. Samples of arterial blood were obtained at 5, 10 and 15 min to analyze for local anesthetic plasma concentrations. Then we infused epinephrine simultaneously with the local anesthetic infusion to determine the arrhythmogenic dose in the presence of local anesthetic (Dose 1). Doses 2 and 3 of each local anesthetic were administered and tested in the same way. In each experiment, each animal received four infusions of epinephrine and three bolus and three infusion doses of a local anesthetic.

One week later, each animal received four infusions of epinephrine according to the same time schedule, but without the addition of local anesthetic drugs. This infusion sequence, identical to that used previously, allowed us to evaluate the consistency of effect of repeated administrations of epinephrine. All data were subjected to multivariant analysis of variance. Duncan's multiple comparison was used to make pairwise comparisons between drugs when a significant F ratio ($P < 0.05$) was obtained.

Results

Arterial plasma concentrations of lidocaine, bupivacaine, and etidocaine and the arrhythmogenic doses

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of epinephrine after each dose of each local anesthetic increased with subsequent doses. With one exception, arrhythmias developed in all animals after epinephrine administration. The exception was one animal in the lidocaine group (Dose 2) that did not have premature ventricular contractions after a total epinephrine dose of 17.7 μg/kg. Since cardiac arrhythmias did occur after the dose with the next highest concentration of lidocaine (Dose 3), we decreased this epinephrine dose from 17.7 to 8.7 μg/kg. This lower dose of epinephrine corresponded to that when the mean arterial pressure reached a maximal value (104 sec). Doses 1 and 2 of all local anesthetics increased significantly the arrhythmogenic dose of epinephrine, but no significant difference among the drugs was observed. There was no difference between Doses 1 and 2 with any drug. However, Dose 3 of all local anesthetics significantly increased the arrhythmogenic dose of epinephrine compared with Doses 1 and 2 of local anesthetics.

Arterial blood-gas values before epinephrine infusion were pH 7.38 ± 0.03, P_{O_2} 471 ± 60 torr, and P_{CO_2} 38 ± 3 torr (mean ± SD). We observed no difference among the drugs in their effects on mean arterial pressure and heart rate at the onset of arrhythmias. Linear regression analysis of plasma levels of local anesthetics and arrhythmogenic doses of epinephrine showed no significant difference among the drugs. By multiplying bupivacaine and etidocaine values by a potency factor of 4, we achieved equipotency of plasma levels.[9]

All animals survived the 18 local anesthetic experiments. However, during the final six, multiple-epinephrine-infusion studies in the absence of a local anesthetic, ventricular fibrillation developed in one dog (epinephrine dose 3.33 μg/kg). The repeated administration of epinephrine according to the same time schedule to five other animals showed no significant change from the control values previously obtained from the local anesthetic experiments. Furthermore, no significant difference in arrhythmogenic threshold occurred with repeated doses of epinephrine. Therefore, we chose to use the initial arrhythmogenic dose determined as the control epinephrine dose for statistical evaluations just before the three local anesthetic administrations.

Discussion

Our findings show that equipotent intravenously administered doses of lidocaine, bupivacaine, and etidocaine have equivalent antiarrhythmic effects in the presence of epinephrine in dogs during halothane anesthesia. Bupivacaine and etidocaine both have antiarrhythmic properties because of their similar structural relationship to lidocaine. By inducing ventricular arrhythmias with either electrical stimulation or digitalis, Boettner[3] and Dunbar[4] and their associates have shown that equipotent doses of lidocaine, bupivacaine, and mepivacaine have equivalent antiarrhythmic actions. Since plasma levels of the drugs were not measured in these studies, further comparison with our work cannot be made. There are no clinical reports on the antiarrhythmic properties of etidocaine, but our study shows its antiarrhythmic effect to be equal to that of lidocaine or bupivacaine.

Johnston, Eger and Wilson[1] showed that the addition of lidocaine, 0.5 per cent (250–400 mg), to an epinephrine solution for oronasal submucosal injection increased the arrhythmogenic dose of epinephrine by approximately 75 per cent in surgical patients anesthetized with halothane. More recently, Horrigan, Eger and Wilson[2] reported that the addition of lidocaine to epinephrine increased the threshold for ventricular irritability as much as 277 per cent dose-dependently during enflurane anesthesia. Presumably, this antiarrhythmic effect results from the systemic absorption of lidocaine. This possibility suggests that it might be desirable to administer an intravenous dose of a local anesthetic simultaneously with epinephrine administered for hemostasis rather than to add a local anesthetic to the epinephrine solution. This method would assure that a therapeutic plasma level of local anesthetic was achieved. For example, a single intravenously administered dose of lidocaine, 1.5 mg/kg, would produce an antiarrhythmic plasma level for 6–10 min,[10] the period when epinephrine-induced arrhythmias are most likely to occur.

It is possible that the pharmacokinetics of local anesthetics may not be the same in man as in the dog. However, the plasma concentrations of local anesthetics administered in our study are similar to those observed after clinical injections of local anesthetics and epinephrine for various regional block procedures. Axillary, intercostal and epidural nerve blocks are often associated with lidocaine plasma concentrations ranging from 2 to 5 μg/ml and bupivacaine and etidocaine levels ranging from 0.5 to 2.0 μg/ml.[11–13] This range of lidocaine plasma concentrations is similar to that reported by Gianelley *et al.*[14] to be effective for the treatment of ventricular irritability in patients who had had myocardial infarction.

Our findings also indicate that relatively low plasma concentrations of local anesthetics are effective in increasing the threshold for epinephrine-induced arrhythmias. Although a significant correlation between plasma concentration and the threshold for epinephrine-induced arrhythmias was found for each amide-type local anesthetic studied, increasing the plasma level of the local anesthetic resulted in a dis-

proportionate increase in the arrhythmogenic threshold. For example, a change in mean lidocaine plasma concentration of more than 300 per cent (Dose 1 *vs.* Dose 3) resulted in only a 37 per cent change in epinephrine dosage. In clinical use, the smallest effective dose of antiarrhythmic drug is desirable, since it would be attended by the least toxicity to other organ systems. The plasma concentrations of the large doses of lidocaine are within the range associated with toxicity. This is an even more cogent argument for using the smallest effective dose possible in the clinical situation. Although we found that lidocaine, bupivacaine, and etidocaine were equally effective as antiarrhythmic agents, the choice of one or the other may be influenced by other factors, such as drug uptake, distribution, and metabolism, that may affect plasma levels of local anesthetics in anesthetized patients.

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