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Effect of Midazolam and Diazepam Premedication on Central Nervous System and Cardiovascular Toxicity of Bupivacaine in Pigs

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To determine the effect of benzodiazepine premedication on central nervous system and cardiovascular effects of bupivacaine, the authors administered toxic doses of bupivacaine to awake spontaneously breathing pigs after intravenous premedication with midazolam (0.06 mg/kg), diazepam (0.15 mg/kg), or saline. Five minutes after administration of one of these solutions, they began an infusion of bupivacaine at 2 $mg \cdot kg^{-1} \cdot min^{-1}$. The bupivacaine infusion was continued until cardiovascular collapse. They then attempted to resuscitate the animals *via* open chest cardiac massage and a standard resuscitation protocol. Premedication with midazolam or diazepam significantly delayed the onset of ventricular dysrhythmias ($P < 0.05$), decreased the incidence of seizures ($P < 0.05$), and prevented the increase in blood pressure and heart rate following bupivacaine infusion ($P < 0.05$). Benzodiazepine premedication did not affect the dose of bupivacaine or the blood concentration required to produce cardiovascular collapse. The ability to resuscitate animals premedicated with midazolam did not differ from control; however, significantly fewer animals premedicated with diazepam were resuscitated ($P < 0.05$). A clinically relevant observation was that almost all animals premedicated with a benzodiazepine progressed directly to cardiovascular collapse without first manifesting seizures. (Key words: Anesthetics, local: bupivacaine. Hypnotics, benzodiazepines: diazepam; midazolam. Toxicity.)

BENZODIAZEPINES are frequently administered as anxiolytics prior to regional anesthesia. Additionally, they raise the seizure threshold, providing protection against central nervous system toxicity of local anesthetics.[1–3] Previous studies of the effect of benzodiazepines on the cardiovascular toxicity of local anesthetics have produced conflicting results. Diazepam, midazolam, and lorazepam raised the LD50 of lidocaine, etidocaine, and bupivacaine in mice.[4] Similarly, diazepam pretreatment decreased ventricular irritability in cats given convulsant doses of lidocaine.[5] By contrast, diazepam has been reported to increase the incidence of serious cardiac dysrhythmias in rats given toxic doses of bupivacaine.[6] In all these studies, either the animals were anesthetized, the tracheas were intubated, or the local anesthetic under study was administered by intraperitoneal injection, making it difficult to generalize these data to clinical practice in humans.

Therefore, we developed a model of bupivacaine toxicity in swine that mimics the clinical situation in which bupivacaine is accidentally injected intravascularly in a patient sedated with a benzodiazepine. We then assessed the effect of benzodiazepine premedication on the central nervous system and cardiovascular system toxicity of bupivacaine.

Materials and Methods

The study was approved by our institutional review committee and follows guidelines of the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

After overnight fast, 30 pigs weighing 14–27 kg were anesthetized with halothane and nitrous oxide in oxygen for insertion of invasive catheters. Both femoral arteries were cannulated with 20-gauge, 12.5 cm catheters (Arrow® model AK-04150). One cannula was used for continuous blood pressure (BP) monitoring (Spectramed® transducer model T4812AD-R), and the other for sampling arterial blood. The right internal jugular vein was cannulated with an 8-Fr central venous introducer with sideport (Arrow® model AK09801) through which a pacing pulmonary artery (PA) catheter (American Edwards® model 93200H-7F) was inserted. The PA catheter was positioned so that a reliable intracardiac electrocardiogram could be continuously monitored. Arterial blood pressure and electrocardiogram were recorded on a strip-chart recorder. The catheter insertion sites were infiltrated with a total of 10 ml of 0.1% (10 mg) bupivacaine. The animals were then suspended in a sling, the anesthetic discontinued, and the animals allowed to breathe room air. The pigs were awake within 15 min and remained quietly in the sling for 1 h. At the end of the hour, either diazepam, 0.15 mg/kg; midazolam, 0.06 mg/kg; or saline, 0.75 ml, was injected intravenously in a blinded randomized fashion (ten animals in each group). This ratio of midazolam to diazepam was based upon previous reports of the relative potencies of these two drugs.[7] Five minutes later, an infusion of 0.75% bupivacaine was begun

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at a rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$ through the proximal port of the PA catheter. During the bupivacaine infusion, the animals were continuously observed for occurrence of tonic/clonic seizures. The bupivacaine infusion was continued until cardiovascular collapse (defined as a mean arterial pressure of 30 mmHg).

At cardiovascular collapse, the trachea was intubated and the lungs ventilated with 100% oxygen. The animals were placed on a table, the chest was opened *via* right thoracotomy, and open chest cardiac massage was performed. Resuscitation continued until successful (defined as stable cardiac rhythm and systolic blood pressure greater than 80 mmHg for 2 min) or until 25 min had elapsed. Resuscitation followed Advanced Cardiac Life Support (ACLS) protocol, except that bretylium replaced lidocaine in treatment of ventricular fibrillation. This was done because of evidence that bretylium is superior to lidocaine in treatment of bupivacaine-induced ventricular fibrillation.[8] In addition, epinephrine was administered to maintain adequate systolic blood pressure during compressions (greater than 90 mmHg), rather than at 5-min intervals as per ACLS protocol (average dose 3.4 mg or 0.37 mg/min).

Arterial blood samples were drawn just prior to premedication for determination of baseline Na^+, K^+, CT^-, Ca^{2+}, total protein, hematocrit (Hct), epinephrine (EPI), norepinephrine (NE), *p*H, Pa_{CO_2}, and Pa_{O_2} values. These same measurements, with the exception of NE and EPI, were repeated at cardiovascular collapse. Analysis for NE and EPI were repeated 5 min after benzodiazepine premedication and 2.5 min after initiating the bupivacaine infusion. In addition to measurement at baseline and at cardiovascular collapse, *p*H, Pa_{CO_2}, and Pa_{O_2} were measured 5 min after premedication to determine if premedication affected ventilation or acid-base status. Similarly, *p*H, Pa_{CO_2}, and Pa_{O_2} were measured 5 min after resuscitation began to determine adequacy of ventilation and acid-base status. Blood was drawn for measurement of plasma free bupivacaine and plasma total bupivacaine levels at the onset of seizure activity and at cardiovascular collapse.

Bupivacaine Analysis

Plasma samples were assayed for total bupivacaine by the method of Mather and Tucker.[9] This involved extraction of the drug from plasma and assay by gas chromatography using a flame ionization detector. Binding of bupivacaine to plasma proteins was determined by separating free from bound drug by centrifugal ultracentrifugation using a Centricon-30® Microconcentrator (Amicon). Before centrifugation, each plasma sample was adjusted to the *p*H that was measured for that blood sample at the time of collection. The protein-free ultrafiltrate was assayed for bupivacaine as described above. Preliminary experiments were performed to demonstrate that non-specific losses of drug by binding to the ultrafiltration apparatus did not occur. The bupivacaine assay had a coefficient of variation of 4.2% and a sensitivity limit of 0.03 μg/ml base.

Catecholamine Analysis

Heparinized blood samples for catecholamine analysis were immediately transferred to tubes containing metabisulfite and disodium ethylenedinitrilotetraacetic acid, thoroughly mixed and placed on ice. Within 30 min, the plasma was collected by centrifugation and stored at −20°C until analysis.

Norepinephrine and epinephrine concentrations were determined by high performance liquid chromatography.¶ This procedure involved addition of an internal standard to the plasma followed by adsorption of the catecholamines and internal standard onto alumina. After washing using a Bioanalytical Systems centrifugal microfilter, the compounds were eluted from the alumina for analysis. The extracted samples were analyzed on a high-performance liquid chromatograph using a C18 phase column and electrochemical detector. This procedure measures plasma concentrations of catecholamines with a reproducibility of approximately 10% at concentrations of 500 pg/ml and has a limit of detection of 50 pg/ml.

Statistical Analysis

The BMDP statistical package program (BMDP® Statistical Software Inc.) for the IBM personal computer was used for all statistical analyses. Differences among the groups for categorical and noncategorical variables were analyzed by one-way analysis of variance (time to first dysrhythmia, time to cardiovascular collapse, seizure incidence, ability to resuscitate, and bupivacaine concentration) or analysis of variance for repeated measures (blood pressure, heart rate, epinephrine concentrations, norepinephrine concentrations). Fisher's Exact Test was used for *post-hoc* testing when analysis of variance indicated a difference among the groups. Results were considered significant for *P* values less than 0.05.

Results

Animal groups did not differ with respect to weight, gender, duration of anesthesia for catheter insertion, or baseline hemodynamic or metabolic variables (tables 1, 2).

¶ LCEC Application note No. 14 from Bioanalytical systems Inc., West Layfayette, Indiana.

TABLE 1. Group Characteristics at Baseline

	Wt (kg)	Gender (m/f)	Duration of Anesthesia (min)	Hct (%)	Total Protein (mq/l)	Na^+ (mm/l)	Cl^- (mm/l)	HCO_3^{-2} (mm/l)	K^+ (mm/l)	Ca^{2+} (mm/l)
Control	22 ± 3	6/4	64 ± 23	31 ± 3	5.2 ± 0.5	141 ± 5	110 ± 5	25 ± 3	4.4 ± 0.6	9.5 ± 0.3
Midazolam	21 ± 4	7/3	61 ± 25	36 ± 6	5.3 ± 0.6	142 ± 4	110 ± 5	25 ± 2	4.3 ± 0.6	9.3 ± 0.8
Diazepam	22 ± 3	8/2	62 ± 25	32 ± 3	5.3 ± 0.5	143 ± 6	111 ± 4	26 ± 4	4.3 ± 0.3	9.8 ± 0.5

Values are mean ± SD. n = 10 for each data point.

Animals in the control group experienced dysrhythmias earlier than animals treated with midazolam or diazepam (fig. 1). Dysrhythmias initially consisted of premature ventricular contractions (PVC) and premature atrial contractions (PAC) that progressed to wide complex tachydysrhythmias. During the first 2 min of the bupivacaine infusion, BP and heart rate (HR) increased in the pigs in the control group but not in those receiving benzodiazepines (table 2).

Cardiovascular collapse resulted from electromechanical dissociation in all animals. Following cardiovascular collapse, all animals progressed from a supraventricular rhythm to ventricular fibrillation or asystole. The dose of bupivacaine required to produce cardiovascular collapse, as well as the plasma total bupivacaine and plasma free bupivacaine concentrations at collapse, did not differ among the groups (table 3). After cardiovascular collapse, fewer animals premedicated with diazepam were resuscitated compared with those premedicated with midazolam ($P = 0.04$) (fig. 2). There was no difference in the ability to resuscitate diazepam premedicated animals compared with control animals, nor was there a difference when comparing midazolam-premedicated animals with the control group.

The incidence of tonic-clonic seizures was 100% among pigs in the control group. There were no seizures among animals premedicated with diazepam ($P < 0.01$ compared with control); two of ten midazolam premedicated animals experienced seizures ($P < 0.01$ compared with control). The plasma concentration of bupivacaine in the control group at onset of seizures was 15.9 ± 2.4 ng/ml.

Epinephrine and norepinephrine plasma concentrations increased in all groups in response to bupivacaine infusion. The amount of increase did not differ significantly among the groups (figs. 3, 4).

In pigs in the control group, serum potassium concentrations increased significantly between baseline (4.4 ± 0.6 $mEq \cdot l^{-1}$) and cardiovascular collapse (5.1 ± 0.7 $mEq \cdot l^{-1}$) ($P = 0.02$), while in the benzodiazepine premedicated groups potassium concentrations did not change. Serum Na^+, Cl^-, Hct, and total protein did not change significantly in any group between baseline and cardiovascular collapse.

Arterial blood gas partial pressures and acid-base status did not change between baseline and 5 min after pretreatment with midazolam, diazepam, or saline. Arterial Pa_{O_2} and *p*H decreased between baseline and cardiovascular collapse, although the changes were not different

TABLE 2. Effects of Benzodiazepine Premedication on Hemodynamic Response to Bupivacaine Infusion in Pigs

	Baseline	5 Min after Premedication	1 Min after Starting Bupivacaine Infusion	2 Min after Starting Bupivacaine Infusion	Cardiovascular Collapse
Systolic BP (mmHg)					
Control	144 ± 15	150 ± 20	151 ± 15	174 ± 22	†
Midazolam	141 ± 20	136 ± 22	136 ± 19	133 ± 24*	†
Diazapam	141 ± 21	138 ± 20	134 ± 18	136 ± 21*	†
Diastolic BP (mmHg)					
Control	77 ± 10	80 ± 10	86 ± 10	114 ± 12	†
Midazolam	72 ± 10	76 ± 12	82 ± 11	82 ± 22*	†
Diazepam	75 ± 15	81 ± 16	83 ± 13	87 ± 15*	
Heartrate (beats/min)					
Control	123 ± 15	136 ± 21	129 ± 20	149 ± 16	103 ± 28
Midazolam	128 ± 16	139 ± 14	128 ± 10	124 ± 13*	85 ± 27
Diazepam	144 ± 20	154 ± 21	137 ± 17	130 ± 13*	84 ± 25

n = 10 for each data point.
Values are mean ± SD.

* $P < 0.05$.
† Mean arterial pressure = 30 mmHg at collapase by definition.

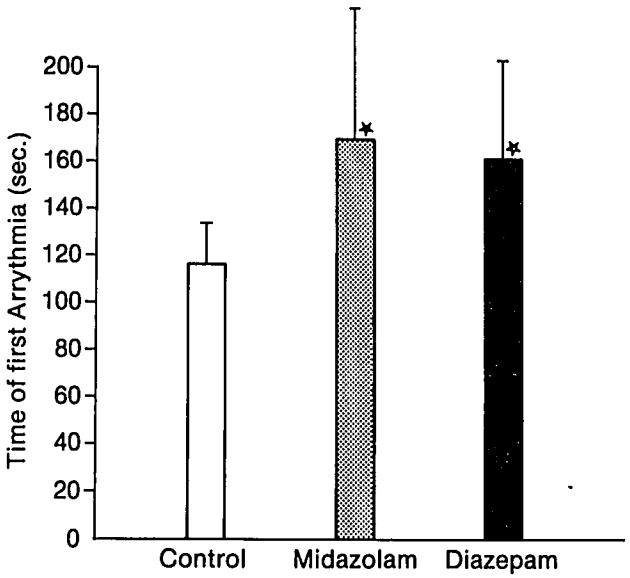

FIG. 1. Effect of premedication with midazolam or diazepam on the time from initiation of intravenous infusion of bupivacaine to the first dysrhythmia. n = 10 for each group (values are mean ± SD). *$P < 0.05$ for diazepam or midazolam compared with control.

among the groups (table 4). Arterial Pa_{CO_2} increased in all groups between baseline and cardiovascular collapse, although to a lesser degree in pigs in the midazolam treated group (table 4).

The times from cardiovascular collapse to tracheal intubation and initiation of open cardiac massage did not differ among the groups, nor did the duration of resuscitation (table 5). Additionally, there was no difference between resuscitated and unresuscitated animals with respect to times from cardiovascular collapse to intubation and initiation of open cardiac massage.

Discussion

Our results demonstrate that premedication with midazolam or diazepam reduces some, but not all, toxic effects

TABLE 3. Effect of Benzodiazepine Premedication on Bupivacaine Cardiovascular Toxicity

	Control	Midazolam	Diazapam
Time from initiating bupivacaine infusion to collapse (s)	252 ± 35	241 ± 59	252 ± 67
Total dose of bupivacaine at collapse (mg/kg)	8.4 ± 1.2	8.0 ± 2.0	8.4 ± 2.2
Plasma total bupivacaine at collapse (μg/ml)	25.7 ± 4.5	25.6 ± 5.1	24.8 ± 6.7
Plasma free bupivacaine at collapse (μg/ml)	9.6 ± 2.7	11.6 ± 3.3	10.0 ± 3.5

Values are mean ± SD. n = 10 for each data point.

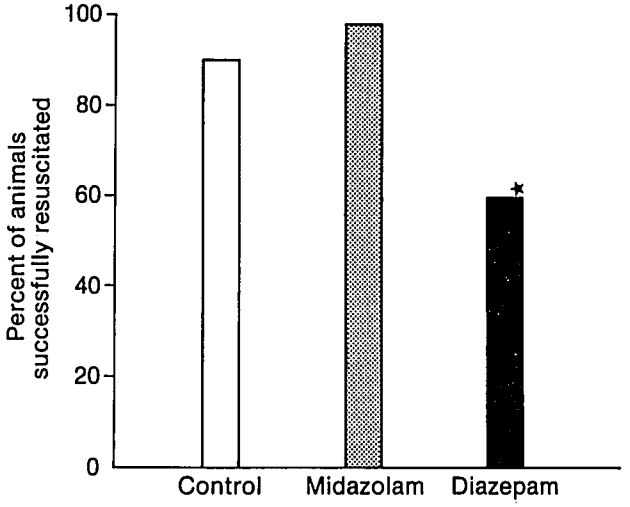

FIG. 2. Effect of premedication with midazolam or diazepam on the ability to resuscitate animals following cardiovascular collapse caused by bupivacaine. $P = 0.04$ for diazepam compared with midazolam. $P > 0.05$ for midazolam and diazepam compared with control.

of bupivacaine on the central nervous system and cardiovascular system. The reduction in CNS toxicity was evident by the lower incidence of seizures in the animals premedicated with a benzodiazepine. This finding is in agreement with previous studies.[1-3] The presence of seizures in all animals in the control group may explain the increase in serum potassium between the baseline measurement and cardiovascular collapse in this group.

Although benzodiazepine premedication suppressed manifestations of bupivacaine CNS toxicity, *i.e.*, seizures, it did not affect the threshold for cardiovascular collapse. If these results can be extrapolated to humans, one must be concerned that patients premedicated with a benzo-

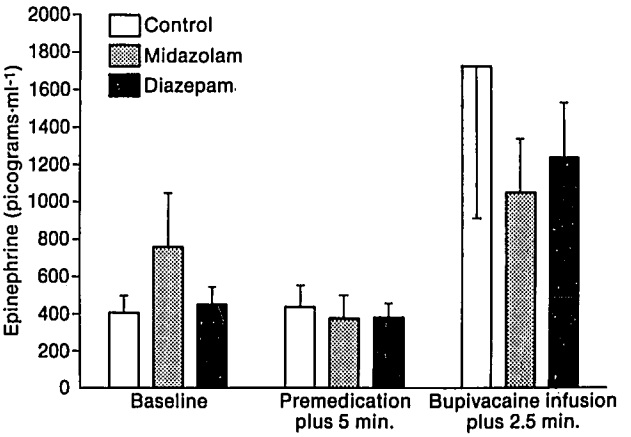

FIG. 3. Effect of premedication with midzolam or diazepam on plasma epinephrine levels 5 min after premedication and 2.5 min after beginning bupivacaine infusion (values are mean ± SD).

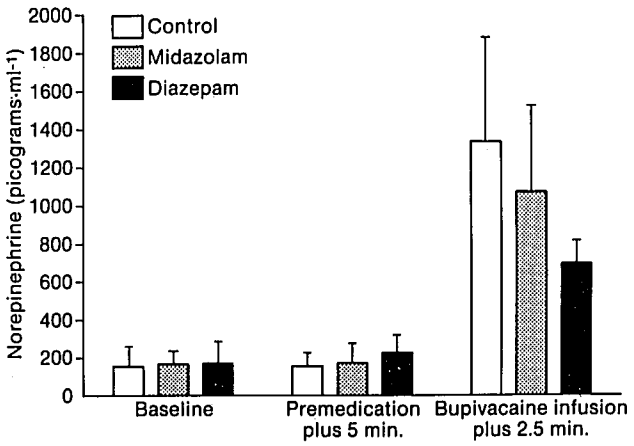

FIG. 4. Effect of premedication with midazolam or diazepam on plasma norepinephrine levels 5 min after premedication and 2.5 min after beginning bupivacaine infusion (values are mean ± SD).

TABLE 4. Effects of Premedication and Bupivacaine Infusion on Arterial Blood Gases

	Baseline	5 Min after Sedation	Cardiovascular Collapse
*p*H			
Control	7.41 ± 0.03	7.42 ± 0.04	7.27 ± 0.07
Midazolam	7.42 ± 0.03	7.40 ± 0.04	7.31 ± 0.04
Diazepam	7.42 ± 0.03	7.42 ± 0.03	7.30 ± 0.05
Pa_{O_2} (mmHg)			
Control	87 ± 7	90 ± 7	26 ± 15
Midazolam	82 ± 11	80 ± 9	26 ± 9
Diazepam	93 ± 8	84 ± 9	22 ± 7
Pa_{CO_2}			
Control	40 ± 3	40 ± 3	57 ± 9
Midazolam	39 ± 3	40 ± 2	51 ± 6
Diazepam	40 ± 4	40 ± 3	58 ± 4

Values are mean ± SD. n = 10 for each data point.

diazepine prior to accidental intravascular injection of bupivacaine may progress directly to cardiovascular collapse without manifesting CNS toxicity as a premonitory sign. Loss of CNS signs of toxicity may delay the institution of appropriate supportive care and, thus, adversely affect outcome.

Benzodiazepine premedication prevented the BP and HR increases in response to bupivacaine infusion and delayed the onset of dysrhythmias. These effects of benzodiazepine premedication on the cardiovascular toxicity of bupivacaine are more complex than the effects on CNS toxicity. This complexity arises because bupivacaine produces cardiovascular system toxicity *via* both direct and indirect mechanisms. Bupivacaine can act directly on the myocardium to produce dysrhythmias, to decrease contractility, and to decrease automaticity.[10,11]** In addition, bupivacaine has been shown to act within the CNS to produce both dysrhythmias and changes in BP and HR.[12,13] We hypothesize that benzodiazepines modify early bupivacaine cardiovascular toxicity by inhibiting cardioactive neurons in the CNS that would otherwise be stimulated by toxic doses of bupivacaine. That is, benzodiazepines may prevent stimulation of sympathetic nervous system neurons by bupivacaine, just as they abolish seizures by preventing bupivacaine mediated stimulation of neurons in the amygdala.[14]

Our results differ from those of Gregg *et al.*, who reported that diazepam premedication decreased the threshold for serious arrhythmias in rats following bupivacaine administration.[6] There are several possible explanations for the conflicting findings of our studies. Gregg *et al.* performed their study using anesthetized rats whose tracheas were intubated, which contrasts sharply with our model using awake, spontaneously breathing pigs. Also, the rats in Gregg's study were more hypercarbic and acidotic even 1 min after starting the bupivacaine infusion than were our animals at any time during our study. Since hypercarbia and acidosis lower the threshold for ventricular irritability,[15] this difference in Pa_{CO_2} and acid-base status may explain the increased toxicity observed by Gregg *et al.*

Though benzodiazepine premedication had no effect on the threshold for cardiovascular collapse, pretreatment with diazepam when compared to midazolam had a negative effect on our ability to resuscitate these animals—all of which died in refractory ventricular fibrillation. We were unable to identify any experimental variable other than differences between the drugs to explain this finding. One possible explanation lies in the fact that the solvent in which diazepam is dissolved (propylene glycol) has been shown to produce hypotension, bradycardia, and ventricular dysrhythmias.[16] It is possible that propylene glycol in some way acted synergistically with bupivacaine to render the myocardium refractory to defibrillation. This explanation seems unlikely, because the dose of propylene glycol administered in this study was much less than that

TABLE 5. Resuscitation Variables

	Control	Midazolam	Diazepam
Time from collapse to intubation (s)	183 ± 151	167 ± 136	201 ± 158
Time from collapse to cardiac massage (s)	268 ± 122	266 ± 141	318 ± 153
Duration of successful resuscitation	524 ± 342	493 ± 362	443 ± 169

Values are mean ± SD. n = 10 each for data point.

** Block AB, Covino BG: Effect of local anesthestic agents on cardiac conduction and contractility. Regional Anesthesia 6:55–61, 1981

which has been shown to produce cardiovascular effects. Additionally, there were no hemodynamic changes following diazepam premedication, and dysrhythmias were delayed by diazepam pretreatment, not hastened by it. Regardless of the mechanism, it appears that, in this model and at this dose ratio, diazepam may be inferior to midazolam as a premedicant in the event of cardiovascular collapse following a toxic dose of bupivacaine.

There are several potential criticisms of our study. We studied only one dose each of midazolam and diazepam and, thus, did not generate a dose-response curve. It is possible that the observed effects of these two drugs would differ significantly at different doses. We infused bupivacaine at a constant rate and not in incremental doses, as is commonly done when injecting peripheral nerves or the epidural space with local anesthetics. As with all animal studies, direct extrapolation of our results to humans is difficult. However, we believe that conditions present in our experimental preparation more closely resemble human physiology and clinical practice than that present in previous studies and, therefore, our results may be more applicable to clinical practice.

In summary, we have studied bupivacaine toxicity in an experimental animal preparation that mimics the clinical situation in which a sedated but awake patient receives a toxic dose of bupivacaine intravascularly. We found that benzodiazepine premedication prevents the initial BP and HR increase induced by intravascular administration of bupivacaine, raises the seizure threshold, and delays the onset of ventricular dysrhythmias. Despite these effects, premedication with midazolam or diazepam does not alter the threshold for cardiovascular collapse secondary to toxic doses of bupivacaine. Diazepam pretreatment resulted in decreased ability to resuscitate animals after cardiovascular collapse. Furthermore, we observed that most benzodiazepine premedicated animals progressed directly to cardiovascular collapse without manifesting premonitory signs of CNS toxicity.

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