Anesthesiology
74:89–96, 1991

Hexamethonium and Midazolam Terminate Dysrhythmias and Hypertension Caused by Intracerebroventricular Bupivacaine in Rabbits

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Previous studies have demonstrated that bupivacaine administered directly into the central nervous system (CNS) is capable of producing signs of bupivacaine cardiovascular toxicity. To investigate the mechanisms by which bupivacaine may act within the CNS to produce cardiovascular toxicity, we studied four groups of halothane-anesthetized rabbits in which infusion of intracerebroventricular (icv) bupivacaine or intravenous (iv) phenylephrine resulted in dysrhythmias and hypertension. In group 1 (n = 5), icv bupivacaine (500 ± 79 μg [mean ± SEM]) produced dysrhythmias lasting 73 ± 13 min, whereas icv saline caused no dysrhythmias or hypertension. In group 2 (n = 9), icv bupivacaine-induced hypertension and dysrhythmias were abolished by icv midazolam in 4.4 ± 0.6 min, and when dysrhythmias and hypertension recurred (22 ± 0.9 min), hexamethonium (10 mg/kg iv) promptly terminated dysrhythmias and hypertension (14 ± 1 s). In group 3 (n = 10), icv bupivacaine-induced dysrhythmias and hypertension were not affected by increasing the inspired halothane concentration from 0.8 to 1.6%. In group 4 (n = 6), iv phenylephrine-induced dysrhythmias and hypertension were not affected by icv midazolam. These results suggest that icv bupivacaine produces dysrhythmias and hypertension by increasing autonomic nervous system (ANS) outflow from the brain stem. The finding that peripheral autonomic blockade by hexamethonium rapidly terminated dysrhythmias and hypertension supports this mechanism. We speculate that icv bupivacaine produces an increase in autonomic outflow by blockade of the inhibitory γ-aminobutyric acid (GABA) neurons that are known to be the principal tonic inhibitors of the ANS. This hypothesis is supported by the finding that CNS GABA potentiation by icv midazolam, but not generalized CNS depression by halothane, terminated dysrhythmias and hypertension. (Key words: Anesthetics, local: bupivacaine. Autonomic nervous system, ganglionic blockers: hexamethonium. Hypnotics, benzodiazepines: midazolam. Toxicity: cardiovascular.)

MOST STUDIES of bupivacaine cardiovascular toxicity have focused on bupivacaine's direct myocardial effects as the mechanism producing cardiovascular toxicity.[1–6] However, there is evidence that bupivacaine may produce cardiovascular toxicity in part by drug actions within central nervous system (CNS). Heavner reported that intracerebroventricular (icv) administration of bupivacaine in unmedicated cats caused ventricular dysrhythmias as well as hypertension and tachycardia.[7] Thomas *et al.* reported that direct application of bupivacaine into autonomic nervous system (ANS) control areas in the rat medulla produced cardiac dysrhythmias, bradycardia, and hypotension.[8] These two studies demonstrate that bupivacaine cardiotoxic effects can be produced by CNS administration of the drug and suggest that the ANS is the route by which these effects are mediated.

Evidence that intravenous bupivacaine administration may produce cardiovascular toxicity by a CNS mechanism comes from a study by Bernards *et al.*[9] These investigators reported that premedication with intravenous (iv) midazolam and diazepam (benzodiazepines that potentiate γ-aminobutyric acid [GABA] activity within the CNS) prevented hypertension and tachycardia and increased the threshold for ventricular dysrhythmias in pigs given toxic iv doses of bupivacaine.

The current study was designed to investigate further the mechanisms by which bupivacaine may act within the CNS to produce cardiovascular toxicity. We developed a rabbit model in which cardiac dysrhythmias and hypertension resulted from icv bupivacaine administration. We then studied the effects of peripheral autonomic ganglion blockade, GABA potentiation within the CNS, and generalized CNS depression on the dysrhythmias and hypertension produced by icv bupivacaine. In addition, to investigate the role of hypertension in icv bupivacaine-induced dysrhythmias, we studied a group of animals in which dysrhythmias were produced by iv phenylephrine infusion. Based on our results and a review of the relevant literature, we propose a model to explain the mechanism whereby icv bupivacaine acts within the CNS to produce cardiovascular toxicity.

Materials and Methods

Animal use was approved by the University of Washington Animal Care Committee. Guidelines of the American Association for Laboratory Animal Care were followed throughout the study.

General Procedure

Thirty New Zealand rabbits, weighing 2.4–4.4 kg, were anesthetized with halothane (1–2%) and N_2O (66%) in O_2. After tracheal intubation, the lungs were ventilated with a Harvard pump. Expired CO_2 was continuously monitored (Beckman LB-2® medical gas analyzer), and

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Received from the Department of Anesthesiology, University of Washington, Seattle, Washington. Accepted for publication August 10, 1990.

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arterial blood gases were measured to verify the accuracy of expired CO_2 measurements. Ventilation was adjusted, as indicated by end-tidal CO_2 measurements, to maintain normocapnia. The right femoral artery was cannulated for blood pressure monitoring and blood sampling. The right femoral vein or an ear vein was cannulated for venous access.

The head was secured with blunt prongs in a stereotactic frame and the skull exposed through a longitudinal scalp incision. A 2-mm burr hole was drilled at a point 5 cm left of the sagittal suture and 5 cm caudad to the coronal suture. A 20-G needle was inserted through this hole into the left lateral ventricle. A T-piece connected to this needle allowed simultaneous perfusion of the ventricle and measurement of ventricular cerebrospinal fluid (CSF) pressure. The posterior neck muscles were dissected and a 20-G cannula was inserted between the first cervical vertebra and the base of the cranium, and into the cisterna magna. A T-piece connected to this cannula allowed collection of the ventriculocisternal perfusate and measurement of cisternal CSF pressure. Continuous measurement of ventricular and cisternal CSF pressure allowed selection of a rate of intraventricular drug administration that did not increase CSF pressure.

Ventriculocisternal perfusion was established by perfusing mock CSF (pH = 7.32; 300 mOsmol/kg) through the ventricular cannula and was considered successful if CSF pressure did not increase above preperfusion values and mock CSF flowed from the cisternal cannula. Ventriculocisternal perfusion was controlled by a syringe pump at a rate of 0.057 ml/min.

Needle electrodes were inserted at both shoulders and both thighs to monitor the electrocardiogram (ECG). The right hemispheric electroencephalogram (EEG) was monitored (Lifescan® Brain Activity Monitoring System, Diatek Medical Technology, San Diego, CA) with the use of gold cup electrodes placed over the right frontal cortex and the parietooccipital cortex. Blood pressure, heart rate, CSF pressure, ECG, and end-tidal CO_2 were continuously recorded on a strip chart recorder. On completion of surgical preparation, N_2O was discontinued; halothane was decreased to 0.8% inspired concentration; and paralysis was initiated by continuous infusion of pancuronium bromide (40–80 μg/h) through the venous cannula. The EEG was continuously monitored as an indicator of anesthetic depth. The predominance of low-frequency activity and the near absence of high-frequency activity indicated that the animals were adequately anesthetized after the decrease in anesthetic depth. After the change in anesthetic, we allowed at least 30 min to elapse before beginning any experiments. A simplified outline of the experimental groups and treatments is presented in table 1.

Group 1: Bupivacaine Alone

In 5 of the 30 rabbits, studies were performed to determine whether the cardiac dysrhythmias that result from icv bupivacaine are the result of bupivacaine's local anesthetic effects or the result of pH, volume, or osmolality effects of the vehicle with which bupivacaine is delivered. In addition, we sought to determine the duration of dysrhythmias induced by icv bupivacaine. All 5 rabbits received 0.1-ml boluses of saline (300 osmol/kg solvent, pH = 7.0) through the ventricular cannula at 5-min intervals to a total dose of 0.5 ml. Blood pressure, heart rate, CSF pressure, ECG, and EEG were monitored continuously. Thirty minutes later, these 5 rabbits received a 0.05-ml bolus of 0.5% bupivacaine (osm = 300; pH adjusted to 7.0by addition of 0.1 N NaOH). If dysrhythmias did not develop after 0.05 ml bupivacaine, 0.1-ml boluses of bupivacaine were administered into the ventricle every 5 min until dysrhythmias occurred. Dysrhythmias were defined as any abnormal ventricular rhythm (*e.g.*, ectopic beats occurring more often than five times per minute, bigeminy, trigeminy, or ventricular tachycardia).

Group 2: Bupivacaine Followed by Midazolam and Hexamethonium

Nine rabbits were surgically prepared as described above, and continuous ventriculocisternal perfusion was begun with 0.5% bupivacaine at a rate of 0.0148 ml/min (79 μg/min). Perfusion was continued until cardiac dysrhythmias developed or 30 min elapsed. The dose of bupivacaine that produced dysrhythmias was calculated as the product of the icv infusion rate and the duration of infusion. At the onset of cardiac dysrhythmias, 4 ml arterial blood was withdrawn for later bupivacaine analysis and ventriculocisternal perfusion was reestablished with

TABLE 1. Experimental Groups and Treatment

Experimental Group	Sequential Treatments			
	1st	2nd	3rd	4th
1 (n = 5)	icv saline	icv Bupivacaine	icv midazolam	iv hexamethonium
2 (n = 9)	icv bupivacaine	icv Saline		
3 (n = 10)	icv bupivacaine	Increased inspired halothane		
4 (n = 6)	iv phenylephrine	icv midazolam		

mock CSF. Whenever dysrhythmias continued for more than 5 min, 0.1 ml saline was administered as a slow bolus (over 30 s) into the left cerebral ventricle. Saline was administered as a *p*H, osmolality, and volume control for the effects of icv midazolam. Ten minutes after administration of saline, if dysrhythmias were still present, 0.1 ml midazolam (1 μg) was administered as a slow bolus into the left lateral ventricle. Midazolam was administered to determine the effect of GABA potentiation within the CNS on dysrhythmias and hypertension produced by icv bupivacaine. Blood pressure, heart rate, CSF pressure, ECG, and EEG were recorded continuously.

In five of the six animals in which dysrhythmias recurred after treatment with midazolam, hexamethonium (10 mg/kg) was administered as an iv bolus. Hexamethonium was administered to determine the effect of peripheral ANS ganglionic blockade on dysrhythmias and hypertension produced by icv bupivacaine. In the remaining one of six animals in which dysrhythmias recurred, a second dose of midazolam was administered into the left lateral ventricle to determine whether the effect of midazolam was reproducible after recurrence of dysrhythmias.

Group 3: Intracerebroventricular Bupivacaine Followed by Increased Inspired Halothane Concentration

Ten rabbits were surgically prepared as described above and received icv bupivacaine (0.5%) at 0.0148 ml/min until dysrhythmias occurred or 15 min elapsed. In animals in which dysrhythmias developed, the inspired halothane concentration was increased from 0.8 to 1.6%. This was done to determine whether the effects of midazolam on mean arterial pressure (MAP) and dysrhythmias were specific to its ability to potentiate GABA within the CNS or whether these effects could be reproduced by any drug that produces nonspecific CNS depression. End-tidal halothane concentrations before and 3 min after increase of the inspired halothane concentration were measured in six rabbits.

Group 4: Intracerebroventricular Mock CSF Followed by Intravenous Phenylephrine

Six animals were surgically prepared as described above and received icv mock CSF (0.0148 ml/min). Twenty minutes after discontinuation of N_2O and decrease of halothane to 0.8% inspired, the animals received an iv phenylephrine infusion (40 μg/ml) at a rate sufficient to maintain MAP between 125 and 150 mmHg. This was done to determine whether or not the dysrhythmias produced by icv bupivacaine were simply the result of an increase in MAP. Ten minutes after the dysrhythmias developed in the animals in response to hypertension produced by iv phenylephrine infusion, 1 μg midazolam was injected into the lateral cerebral ventricle. This was done to determine whether CNS midazolam had the same effect on dysrhythmias produced by iv phenylephrine as it did on dysrhythmias produced by icv bupivacaine.

End-tidal Halothane Concentration Measurement

Each expired gas sample was obtained by collecting 1 ml end-tidal samples from ten consecutive breaths into a single gas-tight glass syringe. Samples were collected from the CO_2 sampling port of the endotracheal tube. Halothane was separated by gas chromatography and the halothane concentration determined with the use of a flame ionization detector (Varian Aerograph® series 1200). This method has a sensitivity of 0.01% and a coefficient of variation of 2.3%.

Bupivacaine Analysis

Plasma samples were assayed for total bupivacaine by the method of Mather and Tucker.[10] This involved extraction of the drug from plasma and assay by gas chromatography with the use of a flame ionization detector. The bupivacaine assay had a coefficient of variation of 4.2% and a sensitivity limit of 0.03 μg/ml base.

Statistical Analysis

Fisher's exact test was used to compare the effect of icv bupivacaine and saline on the incidence of dysrhythmias in rabbits receiving bupivacaine alone (group 1). In rabbits receiving bupivacaine followed by midazolam, Fisher's exact test was used to compare the effect of icv saline and midazolam as treatments for dysrhythmias (group 2). One-way analysis of variance for repeated measures was used to compare MAP and heart rate after icv bupivacaine, after icv midazolam, at the point that dysrhythmias recurred and after iv hexamethonium. Scheffe's F test was used for *post hoc* testing. A pooled *t* test was used to compare differences in time from peak increase in MAP to onset of dysrhythmias between groups 2 and 3 (icv bupivacaine) and group 4 (iv phenylephrine). All results are reported as mean ± standard error. A P value of 0.05 was considered statistically significant.

Results

Group 1: Bupivacaine Alone

In none of the rabbits in this group did ventricular cardiac dysrhythmias develop in response to icv saline, whereas ventricular cardiac dysrhythmias did develop in all five animals after icv bupivacaine ($P = 0.004$). Dysrhythmias consisted of multifocal premature ventricular contractions and ventricular bigeminy. The average dose

of bupivacaine that produced cardiac dysrhythmias was 500 ± 79 μg (0.1 ± 0.016 ml). The duration of bupivacaine-induced dysrhythmias was 73 ± 13 min.

Group 2: Bupivacaine Followed by Midazolam and Hexamethonium

Table 2 depicts the sequence of drug administration and the response of individual animals to each drug. In seven of nine rabbits, ventricular cardiac dysrhythmias developed in response to icv bupivacaine (862 ± 233 μg). The larger average bupivacaine dose and standard error were caused by one rabbit that required 2,072 μg bupivacaine to induce dysrhythmias. Dysrhythmias consisted of multifocal premature ventricular contractions, bigeminy, trigeminy, and brief runs of ventricular tachycardia. In six of the animals in this group, the dysrhythmias were sustained (duration >10 min). In the seventh animal, dysrhythmias lasted 3.1 min. In the six animals with sustained dysrhythmias, icv saline had no effect on the dysrhythmias. However, icv midazolam terminated cardiac dysrhythmias within 4.4 ± 0.6 min in all six ($P = 0.004$, efficacy of midazolam *vs.* saline in terminating dysrhythmias). No animal had EEG evidence of seizures in response to bupivacaine administration.

Two animals did not have cardiac dysrhythmias in response to bupivacaine infusion. These two animals did, however, show significant ECG changes consisting of t-wave inversions in the inferior/lateral leads and negative rotation of the electrical axis.

Plasma bupivacaine concentrations were determined in the seven rabbits in which cardiac dysrhythmias developed after icv bupivacaine. Plasma bupivacaine concentrations were undetectable in two of seven animals at the onset of dysrhythmias. In the five remaining animals, bupivacaine plasma concentrations averaged 0.21 ± 0.12 μg/ml at the onset of dysrhythmias.

TABLE 2. Treatments Received by Individual Group-2 Animals and Their Responses to Treatment

Animal	Dysrhythmias Following Bupivacaine	Dysrhythmias Terminated by:		Dysrhythmias Recurred	Recurrent Dysrhythmias Terminated by Hexamethonium
		NaCl	Midazolam		
1	Yes	No	Yes	Yes	Yes
2	Yes	No	Yes	Yes	Yes
3	Yes	No	Yes	Yes	Yes
4	Yes	No	yes	Yes	Yes
5	Yes	No	Yes	Yes	Yes
6	Yes	No	Yes	Yes	—†
7	Yes*	—	—	NA	—
8	No	—	—	NA	—
9	No	—	—	NA	—

Dash = not administered; NA = not applicable since midazolam not adminsitered.

* Dysrhythmias not sustained.

† Animal received a second dose of midazolam which again terminated dysrhythmias.

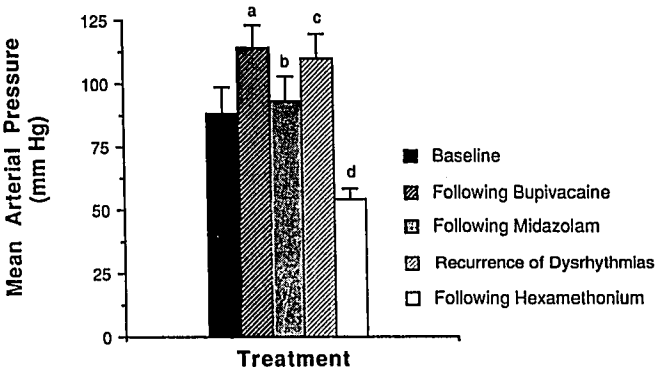

FIG. 1. Change in MAP after icv bupivacaine; after treatment of dysrhythmias and hypertension with icv midazolam; after recurrence of dysrhythmias; and after treatment of dysrhythmias and hypertension with iv hexamethonium. Data are from the five animals that received each treatment and are means ± SE. *a* indicates $P < 0.05$ compared to baseline, midazolam, and hexamethonium; *b* indicates $P < 0.05$ compared to bupivacaine, recurrence of dysrhythmias, and hexamethonium; *c* indicates $P < 0.05$ compared to midazolam, baseline, and hexamethonium; and *d* indicates $P < 0.05$ compared to baseline, bupivacaine, midazolam, recurrence of dysrhythmias, and hexamethonium.

After having initially ceased, dysrhythmias recurred in all six animals that received icv midazolam. The average dysrhythmia-free interval after icv midazolam was 22 ± 0.9 min. Intravenous hexamethonium was administered to five of six animals in which dysrhythmias recurred and promptly terminated dysrhythmias in all five in 14 ± 1 s. The sixth animal received a second dose of midazolam, which terminated dysrhythmias in 3.7 min.

In response to bupivacaine infusion, blood pressure increased significantly above baseline (fig. 1). In animals that received midazolam after development of dysrhythmias, MAP returned to baseline values. In the six animals in which dysrhythmias recurred, MAP again increased significantly above both baseline values and above values after administration of midazolam. In the five animals that received iv hexamethonium after recurrences of dysrhythmias, MAP decreased significantly below baseline. Heart rate averaged 257 ± 25 beats per min at baseline and did not change significantly after any treatment (fig. 2).

There was no difference between CSF pressures at baseline (3.6 ± 1.5 cmH_2O) and at the point of maximal increase in MAP (3.1 ± 1.2 cmH_2O).

Group 3: Intracerebroventricular Bupivacaine Followed by Increased Inspired Halothane Concentration

Dysrhythmias developed in five of ten animals in this group in response to icv bupivacaine. The average dose

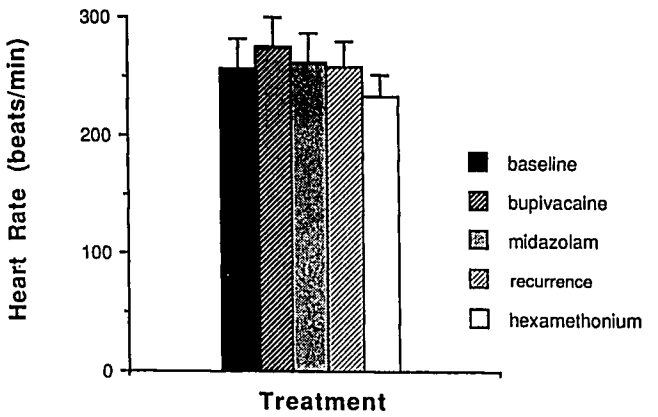

FIG. 2. Change in heart rate after icv bupivacaine, after treatment of dysrhythmias and hypertension with icv midazolam, after recurrence of dysrhythmias, and after treatment of dysrhythmias with iv hexamethonium. Data are from the five animals that received each treatment and are means ± SE. There were no significant differences in heart rate among treatments at any point.

of bupivacaine that produced dysrhythmias was 883 ± 109 μg. The plasma concentration of bupivacaine at the onset of dysrhythmias averaged 0.16 ± 0.05 μg/ml. Increase of the inspired halothane concentration from 0.8 to 1.6% had no effect on dysrhythmias in any of the five animals. An inspired halothane concentration of 0.8% produced a measured end-tidal concentration of 0.73 ± 0.08%, and an increase to 1.6% produced a measured end-tidal concentration of 1.62 ± 0.07% after 3 min.

There was no difference between CSF pressures at baseline (2.2 ± 0.42 cmH_2O) and at the point of maximal increase in MAP (2.1 ± 0.44 cmH_2O).

GROUP 4: INTRACEREBROVENTRICULAR MOCK CSF FOLLOWED BY INTRAVENOUS PHENYLEPHRINE

Ventricular dysrhythmias developed in all six animals in this group in response to iv phenylephrine infusion. Compared with the combined data from groups 2 and 3 (icv bupivacaine), there was no difference in baseline MAP (groups 2 and 3: 83 ± 14 mmHg; group 4: 76 ± 9 [$P = 0.25$]) or maximum MAP (groups 2 and 3: 122 ± 21 mmHg; group 4: 133 ± 16 [$P = 0.24$]). However, the onset of dysrhythmias in the icv bupivacaine-treated groups preceded the maximal increase in MAP by an average of 0.35 ± 0.38 min, whereas in the iv phenylephrine-treated group, the onset of dysrhythmias occurred an average of 4.4 ± 1.3 min after the maximal increase in MAP was reached ($P < 0.0007$). Five of six animals in group 4 received icv midazolam after the onset of dysrhythmias. Midazolam had no effect on dysrhythmias in any of these animals. In contrast, icv midazolam terminated dysrhythmias produced by icv bupivacaine in all six group-2 animals.

There was no difference between CSF pressures at baseline (1.2 ± 0.6 cmH_2O) and at the point of maximal increase in MAP (1.6 ± 0.7 cmH_2O).

Discussion

INTERPRETATION OF RESULTS

Our results demonstrate that icv bupivacaine produces some of the same early signs of cardiovascular toxicity associated with iv bupivacaine administration—namely, ventricular dysrhythmias and hypertension.[9-11] These results are consistent with those of Heavner.[7] The dysrhythmias that we observed are also consistent with the results of Thomas *et al.*[8] Our results (and those of Heavner) differ from the results of Thomas *et al.* with respect to effects on blood pressure. Thomas *et al.* described hypotension after topical application of bupivacaine in a localized area of the rat medulla. This inconsistency may simply be the result of species differences. However, it is more likely that it stems from Thomas *et al.*'s application of bupivacaine to individual sympathetic outflow areas of the medulla instead of simultaneously exposing all sympathetic outflow areas of both the hypothalamus and medulla to bupivacaine, as was done in the current study and the study by Heavner.

The dose of bupivacaine that produced dysrhythmias in group-1 animals is comparable to the dose that produced dysrhythmias in the animals in the study by Heavner (200–800 μg).[7] In animals given bupivacaine by continuous infusion through the ventricular system (groups 2 and 3), we cannot conclude that the dose of bupivacaine reported to produce dysrhythmias necessarily represents the amount of drug acting on brain tissue. Because bupivacaine was administered by continuous infusion, an undetermined fraction of the administered dose may have simply passed through the ventricular system unabsorbed.

Plasma concentrations of bupivacaine, at the onset of dysrhythmias, averaged 0.18 ± 0.05 μg/ml in the 12 animals from groups 2 and 3 in which dysrhythmias developed after icv bupivacaine. These concentrations are well below concentrations (10.83 ± 0.62 μg/ml) found to produce dysrhythmias in rabbits given iv bupivacaine (Bernards and Artru, unpublished data). Therefore, direct myocardial toxicity of bupivacaine is an unlikely explanation for the dysrhythmias that we observed.

The absence of significant change in CSF pressure from baseline during bupivacaine administration or during recurrence of dysrhythmias indicates that the blood pressure increases observed at those times were not the result of increased CSF pressure.

It is unclear what effect anesthesia with halothane and muscle paralysis with pancuronium had on our results. However, because Heavner[7] reported a 100% incidence

of dysrhythmias and blood pressure increases in unmedicated cats given icv injections of bupivacaine, we do not believe that halothane or pancuronium increased the incidence of dysrhythmias or blood pressure increases. We do not know whether the anesthetic used in the current study explains why dysrhythmias did not develop in some animals in response to icv bupivacaine.

Zink *et al.* demonstrated that hypertension during halothane anesthesia is capable of producing cardiac dysrhythmias.[12] Therefore, to determine whether the dysrhythmias produced by icv bupivacaine were simply the result of bupivacaine-induced hypertension, we studied a group of animals in which dysrhythmias were produced by iv phenylephrine infusion. We found that hypertension produced by iv phenylephrine did induce dysrhythmias, but that the time course of those dysrhythmias was significantly different than that produced by icv bupivacaine. Icv bupivacaine-induced dysrhythmias occurred an average of 0.33 min before the maximal increase in MAP, whereas iv phenylephrine-induced dysrhythmias followed the maximal increase in MAP by an average of 4.4 min. These results demonstrate that icv bupivacaine dysrhythmias are coincident with the bupivacaine-induced increase in MAP and are not a result of that increase.

Icv midazolam terminated dysrhythmias and hypertension produced by icv bupivacaine in all five animals in which it was administered. The finding that increasing anesthetic depth with halothane had no effect on dysrhythmias and hypertension produced by icv bupivacaine suggests that the effects of midazolam are specific to its ability to potentiate GABA and not the result of generalized CNS depression. The recurrence of dysrhythmias after they initially ceased in response to icv midazolam likely resulted from a waning of midazolam's effect and reemergence of the unopposed effect of bupivacaine. The recurrence of dysrhythmias is evidence that the initial termination of dysrhythmias after icv midazolam did not result from spontaneous remission.

The occurrence of hypertension and dysrhythmias after icv bupivacaine suggests that these effects are mediated by altered ANS outflow from brain stem autonomic control centers. Prompt termination of dysrhythmias and hypertension by peripheral autonomic blockade with hexamethonium strongly suggests that the ANS is the final pathway mediating these effects. Whether the sympathetic nervous system (SNS) or the parasympathetic nervous system (PNS) is the principal mediator of icv bupivacaine-induced hypertension and dysrhythmias is unclear from the data. The occurrence of dysrhythmias and hypertension without bradycardia would suggest that the SNS is the principal mediator involved. However, there is evidence that dysrhythmias resulting from central autonomic stimulation may result from an interplay between both the PNS and the SNS. Bircher *et al.*[13] demonstrated that brain stem GABA receptor blockade with picrotoxin resulted in both hypertension and dysrhythmias. Bilateral vagotomy prevented dysrhythmias but not hypertension in four of six animals, suggesting that the PNS may be important to the genesis of dysrhythmias in at least some animals.

The rapidity with which hexamethonium terminated dysrhythmias and hypertension (14 ± 1 s) suggests that activity in ANS neurons innervating the myocardium and peripheral vasculature, and not elevated circulating catecholamines, accounts for the observed dysrhythmias and hypertension.

Proposed Model of Intracerebroventricular Bupivacaine-Induced Cardiovascular Changes

Our data suggest that icv bupivacaine produces dysrhythmias and hypertension by altering ANS outflow from the CNS. It is important to ask how a drug that produces neural blockade as its primary action might actually increase the activity of ANS outflow neurons. The neurons that control SNS outflow from the CNS are located in the periventricular hypothalamus and the rostroventrolateral medulla.[14] These SNS outflow neurons are tonically inhibited by local GABA-ergic neurons.[15–17] Neurons controlling parasympathetic outflow to the myocardium reside in the nucleus ambiguus (medulla).[14] Current evidence suggests that parasympathetic outflow in the nucleus ambiguus is also tonically inhibited by GABA-ergic neurons.[18] Local anesthetic-mediated blockade of these inhibitory GABA-ergic neurons would, therefore, explain how icv bupivacaine could increase ANS outflow and in turn produce the dysrhythmias and hypertension that we observed. In other words, just as local anesthetic-mediated blockade of inhibitory cortical neurons results in increased motor neuron outflow (*i.e.*, seizures),[19–21] bupivacaine-mediated blockade of inhibitory GABA-ergic neurons in the brain stem would result in increased ANS outflow. In fact, blockade of brain stem GABA receptors by administration of selective GABA receptor antagonists (*e.g.*, picrotoxin, bicuculline) into the cerebral ventricles results in dysrhythmias and hypertension just as icv bupivacaine does.[13,15,22,23]

Therefore, we hypothesize that icv bupivacaine produces hypertension and dysrhythmias by blocking GABA-ergic neurons that tonically inhibit SNS and PNS outflow. Hypertension then results from increased SNS outflow to the peripheral vasculature. Dysrhythmias result from either an absolute increase in SNS outflow or an imbalance between SNS and PNS outflow to the myocardium. The termination of dysrhythmias and hypertension by both GABA potentiation with midazolam and peripheral ANS blockade with hexamethonium is evidence in support of this model. This proposed mechanism is diagrammed in figure 3.

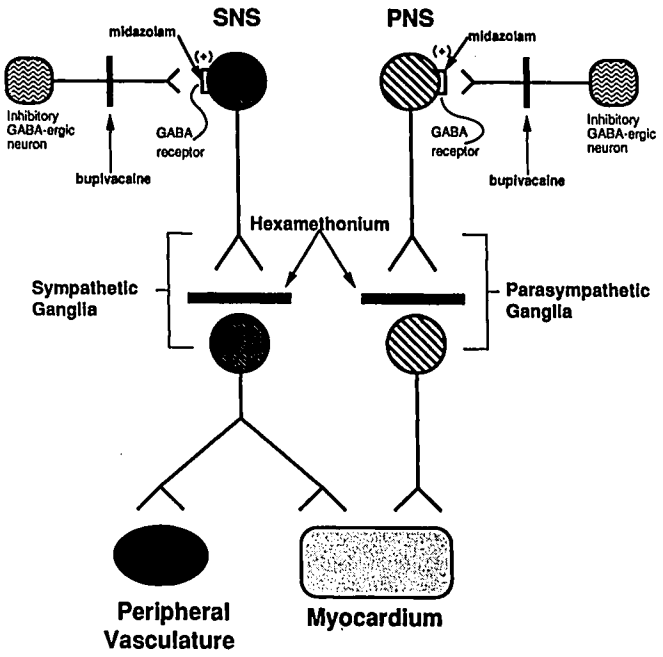

FIG. 3. Proposed mechanism by which icv bupivacaine produces dysrhythmias and hypertension. Bupivacaine produces local anesthetic blockade of GABA-ergic neurons, which tonically inhibit ANS outflow from the brainstem. Increased sympathetic nervous sytem (SNS) outflow to the peripheral vasculature produces hypertension. Increased SNS and possibly PNS outflow to the myocardium produces dysrhythmias. Midazolam terminates dysrhythmias and hypertension by potentiating inhibitory GABA activity at the ANS outflow neurons. Hexamethonium terminates dysrhythmias and hypertension by blockade of peripheral autonomic ganglia. PNS = parasympathetic nervous system.

Our results demonstrate that *icv* bupivacaine is capable of producing dysrhythmias and hypertension. However, it is important to question whether or not *iv* bupivacaine produces any cardiotoxic effects by a CNS mechanism. Evidence that iv bupivacaine may produce some of its cardiotoxic effects by increased ANS outflow from the CNS comes from animal studies of bupivacaine toxicity. Multiple studies have demonstrated early signs of cardiovascular stimulation after toxic intravenous doses of bupivacaine.[9,24–26] Most recently, Rutten *et al.* demonstrated in sheep that bolus iv doses of bupivacaine produced dose-dependent *increases* in MAP, cardiac output, heart rate, systemic vascular resistance, and maximum rate of change in pressure (dP/dt_{max}).[11] Because bupivacaine has clearly been shown to be a direct myocardial depressant,[1–6] the most likely explanation for the cardiovascular stimulation demonstrated in this and other studies is an increase in SNS activity.

We do not mean to suggest that bupivacaine cardiotoxicity after accidental iv administration is produced solely or even principally by a CNS mechanism. Rather, bupivacaine toxicity may be divided into an early stimulatory component (as demonstrated by Rutten *et al.*), which we believe to be CNS-mediated, and a later depressant component that is the result of direct myocardial effects of the drug. Whether or not preventing or treating this early stimulatory component of bupivacaine cardiotoxicity can decrease the morbidity of accidental iv bupivacaine injections remains to be determined. However, because refractory ventricular dysrhythmias are such a prominent part of human bupivacaine toxicity,[27] it is important to investigate further the possibility that early dysrhythmias caused by bupivacaine actions in the CNS may contribute to bupivacaine's late cardiac morbidity.

In conclusion, we have confirmed earlier reports demonstrating that bupivacaine administered directly into the CNS is capable of producing ventricular dysrhythmias and hypertension. Further, we have shown that midazolam terminated dysrhythmias and hypertension presumably by potentiation of GABA receptor activity, whereas hexamethonium terminated dysrhythmias and hypertension by peripheral autonomic blockade. We hypothesize that CNS bupivacaine produces the observed hypertension and dysrhythmias by blockade of GABA-ergic neurons that are normally involved in tonic inhibition of ANS outflow from the CNS. The resultant increase in ANS outflow produces the observed dysrhythmias and hypertension. Our results suggest that iv bupivacaine produces some of its cardiovascular toxicity by a CNS mechanism. Future efforts to develop new methods for treating or preventing bupivacaine toxicity may benefit from consideration of not only the direct cardiovascular toxicity of the drug, but also the CNS effects of bupivacaine.

The authors thank Karen Powers for her expert technical assistance.

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