

## The Effect of Magnesium Sulfate Administration on Cerebral and Cardiac Toxicity of Bupivacaine in Dogs

Dale Solomon, M.D.,\* Leon Bunegin, B.S.,\* Maurice Albin, M.D., M.S.†

The effect of acutely elevated serum magnesium on the CNS and cardiac toxicity of bupivacaine was studied. Anesthesia was induced in mongrel dogs with thiopental, 25 mg/kg, and ventilation was controlled. Sedation was maintained with fentanyl (25  $\mu\text{g/kg}$  bolus and 5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) and pancuronium (0.15 mg/kg bolus and 0.05  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) provided paralysis. Two hours after the thiopental bolus, all animals received an intravenous (iv) infusion of bupivacaine (1  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). The control group (5 animals) received bupivacaine only. The  $\text{Mg}^{++}$  group (5 animals) received  $\text{MgSO}_4$  140 mg/kg iv and 80  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  15 min prior to beginning the bupivacaine infusion. Lead II ECG, cardiac hemodynamics, and two-channel EEG were continuously monitored. Serum magnesium concentrations in the  $\text{Mg}^{++}$  group rose from 0.67 mM (1.3 mEq/L) to 2.42 mM (4.8 mEq/L). The bupivacaine infusion caused PR and QRS interval prolongation in both groups, but QRS widening was greater in the control group. QT interval corrected for heart rate (QTc) lengthened only in the control group. A depression of left ventricular stroke work index (LVSWI) occurred to an equal extent in both groups. The seizure dose of bupivacaine was not different between the two groups:  $12.9 \pm 2.3$  (SEM) mg/kg in the control group and  $13.9 \pm 2.5$  mg/kg in the  $\text{Mg}^{++}$  group. This corresponded to plasma bupivacaine concentrations of  $12.2 \pm 1.8$   $\mu\text{g/ml}$  and  $12.8 \pm 1.4$   $\mu\text{g/ml}$  in the control and  $\text{Mg}^{++}$  groups, respectively. Serious cardiac dysrhythmias occurred at an average bupivacaine dose of  $9.5 \pm 1.7$  mg/kg in the control group but did not occur at all in four of five animals in the  $\text{Mg}^{++}$  group before cardiovascular collapse. Magnesium has cardiac electrophysiologic effects that may explain its ability to suppress bupivacaine-induced cardiac dysrhythmias. (Key words: Anesthetics, local: bupivacaine. Heart: dysrhythmias. Ions: magnesium. Toxicity: bupivacaine.)

MAGNESIUM SULFATE is the therapy of choice for the treatment of preeclampsia in the peripartum period.<sup>1</sup> A large number of patients with preeclampsia also receive regional analgesia for cesarean delivery or attenuation of labor pain.<sup>2,3</sup> Because of its long duration and minimal motor blockade, bupivacaine is often the local anesthetic chosen for epidural analgesia. However, regional analgesia with bupivacaine has been associated with seizures and lethal cardiac dysrhythmias.<sup>4</sup> Avoidance of the use of bupivacaine has been advocated.<sup>5</sup>

The effect of magnesium administration on the CNS and cardiovascular toxicity of bupivacaine has not been

studied. Because of its anticonvulsant properties,<sup>6</sup> magnesium might be expected to increase the convulsant dose of bupivacaine. Magnesium may also protect the heart from the dysrhythmogenic properties of bupivacaine. Bupivacaine causes QT interval (QTI) prolongation on the ECG,<sup>7-9</sup> and like other conditions associated with a prolonged QTI, bupivacaine toxicity can lead to a polymorphic ventricular tachycardia (VT) known as Torsades de Pointes (TdP).<sup>10,11</sup> Magnesium has been shown to be an effective antidysrhythmic in a variety of cases of QTI prolongation and TdP.<sup>12-15</sup> The current study was therefore undertaken in dogs to determine if magnesium would ameliorate the CNS and cardiac toxicity of bupivacaine.

### Materials and Methods

This study received prior approval from the Animal Care and Use Committee of the University of Texas Health Science Center at San Antonio. Ten mongrel dogs of either sex were fasted overnight and anesthetized with 25 mg/kg iv thiopental. Following tracheal intubation the lungs were ventilated to maintain normoxia and normocarbica, and if needed, sodium bicarbonate was administered to obtain a pH of 7.35-7.45. A balloon-tipped thermodilution pulmonary artery catheter was inserted via the femoral vein or external jugular vein for monitoring central venous pressure (CVP), pulmonary artery pressure (PAP), and pulmonary capillary wedge (PCWP) pressures, and cardiac output. A femoral artery was cannulated for continuous blood pressure monitoring and blood sampling. Normothermia was maintained with heating blankets. Prior to the experimental period, the PCWP was increased to 5-7 mmHg with an infusion of hetastarch. Lead II of the ECG, systemic arterial pressure, PAP, CVP, and two-channel EEG (through needle scalp electrodes) were continuously monitored and recorded on a Grass polygraph.

After instrumentation fentanyl (25  $\mu\text{g/kg}$  iv) was administered followed by a 5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  maintenance infusion. All animals were paralyzed with pancuronium (0.15 mg/kg iv with infusion of 0.05  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). A combination of low-dose fentanyl with pancuronium has been shown to have minimal effects on the cardiac conduction system in the dog.<sup>16</sup>

The ten animals were randomly assigned to two groups. In both groups an infusion of iv preservative-free bupivacaine was begun at the rate of 1  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  starting 2 h after the thiopental bolus. The control group received

\* Assistant Professor of Anesthesiology.

† Professor of Anesthesiology and Neurosurgery.

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Address reprint requests to Dr. Solomon: Department of Anesthesiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284-7838.

bupivacaine only. Fifteen minutes prior to starting the bupivacaine infusion, the  $Mg^{++}$  group was made hypermagnesemic by the iv administration of magnesium sulfate, 140 mg/kg, followed by an infusion of  $80 \text{ mg} \cdot \text{kg}^{-1} \text{ h}^{-1}$ .

In both groups thermodilution cardiac outputs (Instrumentation Laboratory 601 cardiac output computer) were determined in duplicate with ice-cold 5% dextrose in water prior to and every 3 min after starting the bupivacaine infusion. The LVSWI was derived from the cardiac output, mean arterial pressure (MAP), PCWP, body surface area, and ECG. Arterial blood was sampled for serum  $Mg^{++}$ ,  $Ca^{++}$ , and  $K^+$  concentrations just prior to starting the bupivacaine infusion in both groups, prior to the magnesium infusion in the  $Mg^{++}$  group, and in both groups at onset of seizure and onset of cardiovascular collapse. Serum magnesium determinations were performed using a DuPont ACA IV Discrete Clinical Analyzer®, using a methylthymol blue complexometric technique. Serum potassium was assayed by a Instrumentation Laboratory system 501 analyzer®. Ionized calcium was determined by a NOVA Biomedical NOVA 2 analyzer®. Arterial blood gases were performed on an Instrumentation Laboratory 1312 Blood Gas Manager®.

Arterial blood was sampled for bupivacaine at the onset of seizure activity and onset of cardiovascular collapse. Because cardiac dysrhythmias were diagnosed on the ECG strip records after the experiment, bupivacaine concentrations were not obtained at the onset of cardiac dysrhythmias. The blood samples were immediately spun and the plasma was frozen. Plasma bupivacaine concentrations were later determined by high performance liquid chromatography (HPLC) using a Waters liquid chromatograph and a 35- $\mu\text{l}$  injection. Bupivacaine standard concentrations of 2.5–40.0  $\mu\text{g}/\text{ml}$  were used to generate a standard curve, and etidocaine HCL served as the internal standard. A linear standard curve was obtained over the range of standard concentrations used with an  $R$  value of 1.0.

Onset of seizure was evidenced by cerebral high amplitude spike activity on the EEG, and the amount of bupivacaine infused to that point was noted. The ECG recordings were examined by a cardiologist who was blinded to treatment, and the onset of serious cardiac dysrhythmias (defined as  $>1^\circ$  A-V block, atrial or ventricular ectopy and junctional or ventricular tachycardia) was noted. The bupivacaine infusion was continued until the MAP was less than 40 mmHg, which was defined as cardiovascular collapse.

Student's  $t$  test was used to determine differences between the two groups in the bupivacaine dose or plasma concentration that caused seizure or cardiovascular collapse. A one-tailed Fisher's exact test was used to determine whether cardiac dysrhythmias occurred more frequently in the control group. One-way analysis of variance

was used to determine differences between groups at the same dose of bupivacaine, and Student's paired  $t$  test was used to determine differences in recorded parameters in the same group at different doses of bupivacaine. Level of statistical significance was set at  $P < 0.05$ . All values are reported as mean  $\pm$  SEM.

## Results

Prior to the experimental period the control and  $Mg^{++}$  groups did not differ in ECG intervals, heart rate, MAP, LVSWI, or electrolytes (table 1). The magnesium bolus and infusion in the  $Mg^{++}$  group resulted in an elevation of serum magnesium levels from a baseline mean of  $0.67 \pm 0.03 \text{ mM}$  ( $1.3 \pm 0.06 \text{ mEq/l}$ ) to a mean of  $2.42 \pm 0.18 \text{ mM}$  ( $4.8 \pm 0.36 \text{ mEq/l}$ ) after 15 min with no change in other measured cations (table 1). The  $Mg^{++}$  concentrations in the  $Mg^{++}$  group had a mean value of 2.40 mM at onset of seizure and 2.56 mM at cardiovascular collapse.

All animals in both groups maintained a sinus cardiac rhythm until at least 6 mg/kg bupivacaine had been infused. Thus, ECG intervals and hemodynamic measurements were compared between groups only up to this dose level. The bupivacaine infusion resulted in PR and QRS interval prolongation in both groups (fig. 1). PR interval prolongation was not statistically different in the two groups by the time 6 mg/kg bupivacaine had been infused. Widening of the QRS complex in the control group occurred after the infusion of 3 mg/kg bupivacaine, but in the  $Mg^{++}$  group there was no significant QRS prolongation until the 6 mg/kg level had been attained. By then QRS widening in the  $Mg^{++}$  group was statistically evident, but the QRS complex in the control group had lengthened significantly more than in the  $Mg^{++}$  group. The QTI corrected for heart rate ( $QTI_c$ ) lengthened from baseline only in the control group, but the  $QTI_c$  in the two groups only approached significance ( $P < 0.06$ ) at 6 mg/kg.

Both groups experienced a diminution in myocardial contractility as evidenced by decreased LVSWI that was not significantly different between the two groups (table 1). An increase in the PCWP in both groups occurred along with evidence of myocardial depression.

The dose of bupivacaine at which EEG evidence of seizure activity was observed did not differ between the two groups and occurred at a mean bupivacaine dose of  $12.9 \pm 2.3 \text{ mg/kg}$  in the control group and  $13.9 \pm 2.5 \text{ mg/kg}$  in the  $Mg^{++}$  group (fig. 2). This corresponded to plasma bupivacaine concentrations of  $12.2 \pm 1.8 \mu\text{g}/\text{ml}$  and  $12.8 \pm 1.4 \mu\text{g}/\text{ml}$  in the control and  $Mg^{++}$  groups, respectively.

The control group suffered cardiac dysrhythmias to a greater extent than the  $Mg^{++}$  group ( $P = 0.024$ ). These dysrhythmias occurred prior to or simultaneously with

TABLE 1. Effect of Bupivacaine on Physiologic Parameters

	Group	Bupivacaine Dose (mg/kg)		
		0 (baseline)	3	6
HR (beats/min)	Control	146 ± 7	131 ± 11*	132 ± 8*
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	145 ± 12		
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	150 ± 8	144 ± 6	133 ± 7†‡
MAP (mmHg)	Control	135 ± 9	140 ± 8	138 ± 13
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	121 ± 5		
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	127 ± 5†	132 ± 7	131 ± 8
PCWP (mmHg)	Control	6.0 ± 0.5	9.4 ± 0.08*	12.8 ± 0.5*†‡
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	5.0 ± 0.03		
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	5.0 ± 0.8	10.0 ± 2.0*	13.4 ± 2.3*†‡
LVSWI (g M/m <sup>2</sup> /beat)	Control	58.9 ± 9.3	51.2 ± 7.8	44.4 ± 8.7*†‡
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	66.4 ± 4.7		
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	61.9 ± 6.1	55.2 ± 4.6*	51.0 ± 5.0*
Serum Mg <sup>++</sup> (mM)	Control	0.67 ± 0.03	—	—
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	0.67 ± 0.04	—	—
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	2.42 ± 0.18†	—	—
Ionized serum Ca <sup>++</sup> (mM)	Control	1.03 ± 0.14	—	—
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	1.14 ± 0.13	—	—
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	1.09 ± 0.13	—	—
Serum K <sup>+</sup> (mEq/l)	Control	2.68 ± 0.04	—	—
	Mg <sup>++</sup> (before MgSO <sub>4</sub> )	2.68 ± 0.11	—	—
	Mg <sup>++</sup> (after MgSO <sub>4</sub> )	2.52 ± 0.11	—	—

Values are mean ± SEM. *P* < 0.05.

\* Different from baseline.

† Different from Mg<sup>++</sup> (before MgSO<sub>4</sub>).

‡ Different from 3 mg/kg bupivacaine.

onset of seizure activity in four of five animals. The types of dysrhythmias and the onset of seizure activity are listed in table 2. Animal 4 in the control group developed severe dysrhythmia-associated hemodynamic compromise, which caused cardiovascular collapse prior to the onset of seizure. Except for multifocal PVC the dysrhythmias experienced by the control group were hemodynamically significant, causing a greater than 30% decrease in the MAP. However, the hemodynamically significant dysrhythmias were transient in all but animal 4, and except for animal 4 cardiovascular collapse was caused by gradual myocardial depression and onset of hypotension. In animals 1–3 the hemodynamically significant dysrhythmias resolved to either sinus or junctional tachycardia with an improvement in blood pressure.

In the Mg<sup>++</sup> group four of five animals remained in sinus rhythm throughout the experimental period. The other (animal 4) developed a wandering atrial pacemaker prior to cardiovascular collapse. In all animals in the Mg<sup>++</sup> group, sinus rhythm continued after the onset of seizure activity and cardiovascular collapse was caused by a progressive diminution in cardiac index and LVSWI, which eventually caused a MAP less than 40 mmHg.

The two groups did not differ in the dose of bupivacaine causing cardiovascular collapse, which occurred at 26.8 ± 5.6 and 30.7 ± 4.2 mg/kg in the control and Mg<sup>++</sup> groups, respectively. This corresponded to plasma bupivacaine concentrations of 23.3 ± 5.5 µg/ml and 31.0 ± 2.6 µg/ml in the control and Mg<sup>++</sup> groups, respectively, which was not statistically different. However, the dose

or plasma level of bupivacaine causing cardiovascular collapse was statistically greater than that causing seizure only in the Mg<sup>++</sup> group (fig. 2).

## Discussion

In this study acute hypermagnesemia (to a mean serum magnesium level of 2.42 mM) did not increase the convulsant dose of bupivacaine but was effective in preventing the cardiac dysrhythmias associated with bupivacaine toxicity in dogs. The serum magnesium concentrations attained with the MgSO<sub>4</sub> bolus and infusion mimic the recommended magnesium levels for treatment of pre-eclampsia.<sup>17</sup>

The mechanism of bupivacaine-induced cardiac dysrhythmias may be multifactorial and probably results from the effects of bupivacaine on the cardiac action potential and conducting system. Slowing of V<sub>max</sub> of the cardiac action potential<sup>7,18,19</sup> and subsequent slowed conduction creates conditions that allow the occurrence of unidirectional block and reentry, leading to ventricular ectopy.<sup>5,20</sup> Slowing of cardiac conduction by bupivacaine has been demonstrated in various intact animal and isolated heart preparations.<sup>7,9,10,21</sup> In the current study slowing of cardiac conduction in the control group was demonstrated by 24%, 59%, and 19% lengthenings of the PR, QRS, and QTc intervals, respectively, after the infusion of 6 mg/kg bupivacaine.

In the current study magnesium prevented some of the QRS widening caused by bupivacaine, whereas A-V

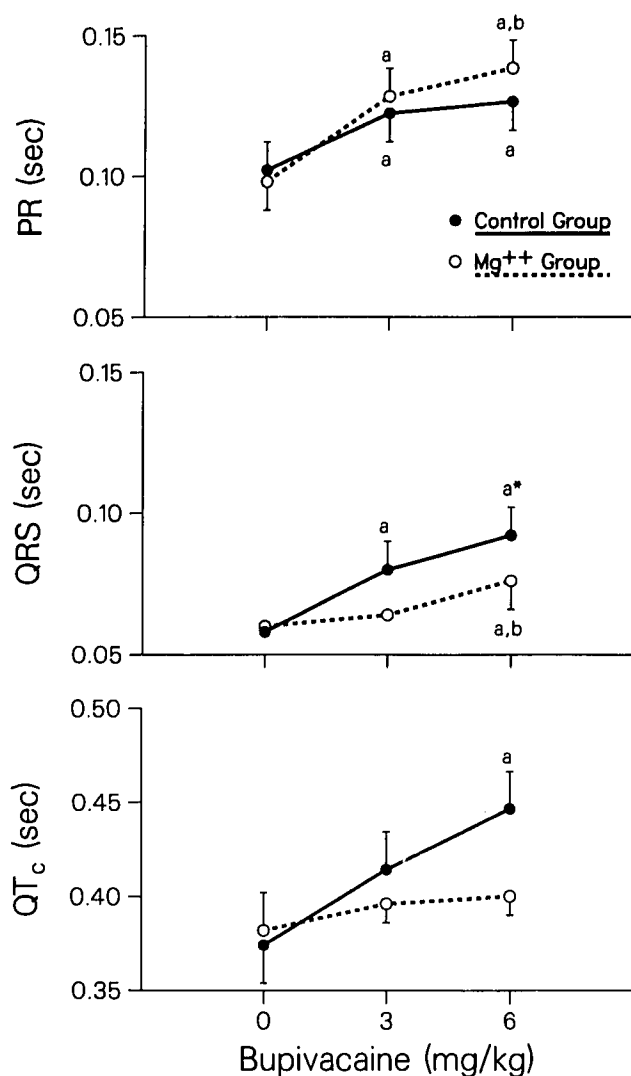


FIG. 1. The effect of bupivacaine infusion on the PR, QRS, and QT<sub>c</sub> intervals of the ECG. a = different from 0 mg/kg; b = different from 3 mg/kg. \*Difference between control and Mg<sup>++</sup> groups.  $P < 0.05$ .

nodal conduction was slowed equally in the two groups (PR interval prolongation caused by magnesium or bupivacaine is caused primarily by slowed A-V nodal conduction<sup>21,22</sup>). This may demonstrate a differential effect of magnesium on A-V nodal and Purkinje-ventricular tissue. Magnesium administration to humans with normal conducting systems lengthens only the PR interval, not the QRS.<sup>22</sup> Magnesium may lessen the effect of bupivacaine on the slowing of cardiac conduction by making the resting membrane potential more negative,<sup>23</sup> by increasing  $V_{max}$ ,<sup>24,25</sup> or by shortening cardiac action potential duration.<sup>24,26,27</sup>

Perhaps the most important effect of bupivacaine on induction of cardiac dysrhythmias is QT<sub>I</sub> prolongation and increased temporal dispersion of the effective refractory period.<sup>28</sup> As with other conditions associated with a prolonged QT<sub>I</sub>, this can lead to TdP.<sup>11-15</sup>

Prior magnesium administration in the Mg<sup>++</sup> group prevented the QT<sub>I</sub> prolongation caused by bupivacaine, which the control group experienced. By preventing prolongation of the QT<sub>I</sub>, magnesium may lessen the dispersion of QT<sub>I</sub> and create fewer opportunities for reentrant-type dysrhythmias to establish themselves. This has been suggested as the basis of the antidysrhythmic action of magnesium in TdP.<sup>12</sup>

Up to bupivacaine doses (6 mg/kg) twice those used clinically, there was no difference in myocardial performance between the two groups, although both groups had evidence of myocardial depression (24.6% and 17.6% decreases in LVSWI in the control and magnesium groups, respectively, table 1). This is significant because magnesium is thought to depress calcium currents<sup>27</sup> and might enhance the myocardial depression caused by bupivacaine, which may also have calcium channel-blocking properties.<sup>29,30</sup>

Of interest in our experiments is the finding that even though serious cardiac dysrhythmias occurred during bupivacaine administration in the control group, these dys-

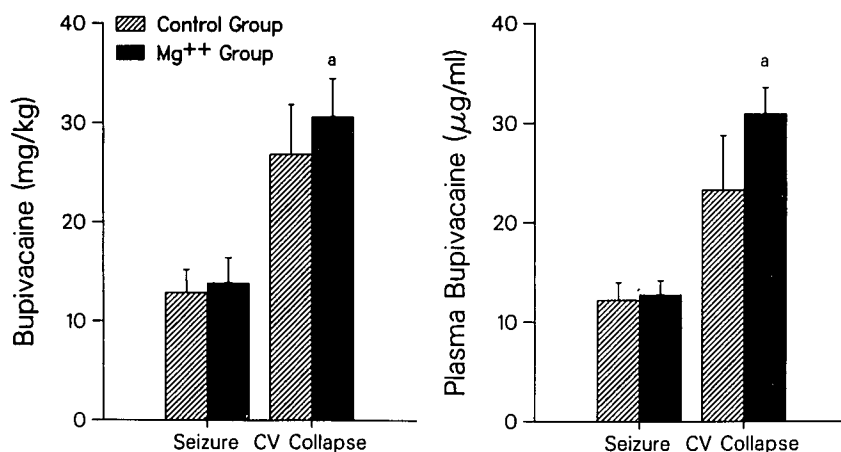


FIG. 2. The iv dose (mg/kg) and plasma concentrations ( $\mu\text{g/ml}$ ) of bupivacaine causing seizure and cardiovascular collapse in the two groups. a = different from seizure.  $P < 0.05$ .

TABLE 2. Bupivacaine Dosages Required to Produce Seizure and Cardiac Dysrhythmia

	Animal	Bupivacaine Infused (mg/kg) to Produce			MAP Decrease >30%
		Seizure	Dysrhythmia	Type	
Control group	1	16.3	6.0	Ventricular tachycardia (transient, 45 s)	Yes
	2	10.5	10.5	Ventricular tachycardia (transient, 25 s)	Yes
	3	7.5	8	Wide complex tachycardia (transient, 40 s)	Yes
	4	10.2	7.5	Wide complex tachycardia (sustained)	Yes
	5	20	15.5	Multifocal PVC (sustained)	No
		12.9 ± 2.35	9.5 ± 1.75		
Mg <sup>++</sup> group	1	19.3	None before CV collapse		NA
	2	14.3	None before CV collapse		NA
	3	8.3	None before CV collapse		NA
	4	19.5	36, wandering atrial pacemaker		No
	5	8.0	None before CV collapse		NA
		13.9 ± 2.5			

rhythmias were with one exception either hemodynamically significant but transient or were sustained but had little effect on blood pressure. Thus, the animals in the control group, except for animal 4, were able to maintain blood pressure after the onset of the dysrhythmia (or after it had resolved) and thereafter, like the Mg<sup>++</sup> group, had a slowly decreasing LVSWI and blood pressure, which eventually led to cardiovascular collapse at a total bupivacaine dose and plasma concentration, which did not differ significantly from the Mg<sup>++</sup> group. Only one animal (number 4) in the control group had a sustained dysrhythmia, which led quickly to cardiovascular collapse. The reason for the transient nature of the serious dysrhythmias in the control group is unknown, but it can be speculated that the continued infusion of bupivacaine caused further conduction blockade and interruption of reentrant dysrhythmias.

Cardiovascular collapse occurred at a total bupivacaine dose of approximately 30 mg/kg in both groups. This is a higher dose than that causing cardiovascular collapse in other studies,<sup>31,32</sup> and may be related to a higher adrenergic tone in our lightly anesthetized dogs.

Only in the Mg<sup>++</sup> group was the dose (or plasma concentration) of bupivacaine that caused cardiovascular collapse significantly greater than that which caused seizure. This would suggest that the administration of bupivacaine is safer when serum magnesium is elevated because CNS toxicity would become evident prior to cardiovascular toxicity.

In the current study magnesium did not increase the plasma concentration of bupivacaine which caused cerebral seizure activity and was an unexpected finding that may be explained in one of several ways. Despite its clear-cut clinical efficacy in treating the seizures of eclampsia,<sup>33</sup>

there is some question whether magnesium has a central anticonvulsant effect.<sup>34</sup> Because magnesium increases cerebral blood flow,<sup>17</sup> our findings may be explained by an increased transport of bupivacaine to cerebral tissue, which overcame any anticonvulsant effects of Mg<sup>++</sup>. The dose of bupivacaine that caused seizures in our animals was significantly higher than that found by Avery *et al.*<sup>32</sup> (5.1 mg/kg in dogs anesthetized with morphine and N<sub>2</sub>O), Liu *et al.*<sup>35</sup> (5.0 mg/kg in awake dogs), and Sage *et al.*<sup>36</sup> (3.4–5.1 mg/kg in conscious dogs). None of these studies employed a barbiturate, and although 2 h had elapsed between the injection of pentothal and the infusion of bupivacaine in our study, there may have been enough residual pentothal in brain tissue to counteract the epileptogenic effects of the bupivacaine. Thus, we are reluctant to say there is no effect of magnesium on the convulsant dose of bupivacaine.

Pregnant patients are relatively hypomagnesemic.<sup>37,38</sup> Like bupivacaine overdose, hypomagnesemia is associated with QTI prolongation and TdP ventricular tachycardia.<sup>13,15</sup> Thus, hypomagnesemia may enhance the cardiotoxicity of bupivacaine. This may partially explain the increased susceptibility of the pregnant patient to the cardiotoxic effects of bupivacaine.

How magnesium is able to reduce the incidence of bupivacaine-induced cardiac dysrhythmias remains speculative. Cardiac electrophysiologic studies of the effect of magnesium on conduction defects caused by bupivacaine appear warranted. This may also elucidate the mechanism of antidysrhythmic effects of magnesium on other syndromes associated with QTI prolongation.

In conclusion, prior magnesium administration appears to be efficacious in diminishing the cardiac dysrhythmogenic properties of bupivacaine in dogs.

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## References

1. Watson KV, Molsow CF, Ogburn PL, Jacob HS: Magnesium sulfate: Rationale for its use in preeclampsia. *Proc Natl Acad Sci USA* 83:1075-1078, 1986
2. Moore TR, Key TC, Reisner LS, Resnik R: Evaluation of the use of continuous lumbar epidural anesthesia for hypertensive pregnant women in labor. *Am J Obstet Gynecol* 152:404-412, 1985
3. Sibai BM, Spinnato JA, Watson DL, Hill GA, Anderson GD: Pregnancy outcome in 303 cases with severe preeclampsia. *Obstet Gynecol* 64:319-325, 1984
4. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine (editorial). *ANESTHESIOLOGY* 51:285-287, 1979
5. Atlee JL III: Perioperative cardiac dysrhythmias: Mechanisms, Recognition, Management. Chicago, Yearbook, 1985, p 176
6. Dinsdale HB: Does magnesium sulfate treat eclamptic seizures? Yes. *Arch Neurol* 45:1360-1361, 1988
7. Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. *Reg Anaesth* 6:55-61, 1981
8. Nath S, Haggmark S, Johansson G, Reiz S: Differential depressant and electrophysiologic cardiotoxicity of local anesthetics: An experimental study with special reference to lidocaine and bupivacaine. *Anesth Analg* 65:1263-1270, 1986
9. D'Athis F, Eledjam JJ, de la Coussaye JE, Brugada J, Desch G, Sassine MDA: Does bupivacaine cardiotoxicity impede only the sodium channels? (abstract). *ANESTHESIOLOGY* 67:A275, 1987
10. Kasten GW, Martin ST: Bupivacaine cardiovascular toxicity: Comparison of treatment with bretylium and lidocaine. *Anesth Analg* 64:911-916, 1985
11. Smith WM, Callaghan JJ: "Les Torsades de Pointes:" An unusual ventricular arrhythmia. *Ann Intern Med* 93:578-584, 1980
12. Tzivoni D, Keren A, Cohen AM, Loebel H, Zahavi I, Cherrybraun A, Stern S: Magnesium therapy for torsades de pointes. *Am J Cardiol* 53:528-530, 1985
13. Levine SR, Crowley TJ, Hai HA: Hypomagnesemia and ventricular tachycardia. *Chest* 81:244-247, 1982
14. Perticone F, Adinolfi L, Bonaduce D: Efficacy of magnesium sulfate in the treatment of torsade de pointes. *Am Heart J* 112:847-849, 1986
15. Ramee SR, White CJ, Svinarich JT, Watson TD, Fox RF: Torsade de pontes and magnesium deficiency. *Am Heart J* 109:164-167, 1985
16. Royster RL, Keeler DK, Haisty WK, Johnston WE, Prough DS: Cardiac electrophysiologic effects of fentanyl and combinations of fentanyl and neuromuscular relaxants in pentobarbital-anesthetized dogs. *Anesth Analg* 67:15-20, 1988
17. Skaredorff MN, Roof ER, Datta S: Hypermagnesemia and anesthetic management. *Can Anaesth Soc J* 29:35-41, 1982
18. Moller RA, Covino BG: Cardiac electrophysiologic effects of lidocaine and bupivacaine. *Anesth Analg* 67:107-114, 1988
19. Clarkson CW, Hondeghem LM: Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. *ANESTHESIOLOGY* 62:396-405, 1985
20. Reiz S, Nath S: Cardiotoxicity of local anesthetic agents. *Br J Anaesth* 58:736-746, 1986
21. Hotvedt R, Refsum H, Helgesen KG: Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dog. *Anesth Analg* 64:388-394, 1985
22. Kulick DL, Hong R, Ryzen E, Rude RK, Rubin JN, Elkayam U, Rahimtoola SH, Bhandari AK: Electrophysiologic effects of intravenous magnesium in patients with normal conduction systems and no clinical evidence of significant cardiac disease. *Am Heart J* 115:367-373, 1988
23. Woods WT, Katholi RE, Urthaler F, James TN: Electrophysiological effects of magnesium on cells in the canine sinus node and false tendon. *Circ Res* 44:182-188, 1979
24. Shine KI: Myocardial effects of magnesium. *Am J Physiol* 237:H413-H423, 1979
25. Watanabe Y, Dreifus LS: Electrophysiologic effects of magnesium and its interactions with potassium. *Cardiovasc Res* 6:79-88, 1972
26. Shattock MJ, Hearse DJ, Fry CH: The ionic basis of the anti-ischemic and anti-arrhythmic properties of magnesium in the heart. *J Am Coll Nutr* 6:27-33, 1987
27. Iseri LT, French JH: Magnesium: Nature's physiologic calcium blocker. *Am Heart J* 108:188-193, 1984
28. Kasten GW: Amide local anesthetic alterations of effective refractory period temporal dispersion: Relationship to ventricular arrhythmias. *ANESTHESIOLOGY* 65:61-66, 1986
29. Lynch C: Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. *Anesth Analg* 65:551-559, 1986
30. Coyle DE, Sperelakis N: Bupivacaine and lidocaine blockade of calcium mediated slow action potentials in guinea pig ventricular muscle. *J Pharmacol Exp Ther* 2:1001-1005, 1987
31. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. *Anesth Analg* 61:317-322, 1982
32. Avery PA, Redon D, Schaenzer G, Rusy B: The influence of serum potassium on the cerebral and cardiac toxicity of bupivacaine and lidocaine. *ANESTHESIOLOGY* 61:134-138, 1984
33. Pritchard JA: The use of magnesium sulfate in preeclampsia-eclampsia. *J Reprod Med* 23:107-114, 1979
34. Koontz WL, Reid KH: Effect of parental magnesium sulfate on penicillin-induced seizure foci in anesthetized cats. *Am J Obstet Gynecol* 153:96-99, 1985
35. Liu PL, Feldman HS, Giasi R, Patterson MR, Covino BG: Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine administration. *Anesth Analg* 62:375-379, 1983
36. Sage DJ, Feldman HS, Arthur GR, Doucette AM, Norway SB, Covino BG: The cardiovascular effects of convulsant doses of lidocaine and bupivacaine in the conscious dog. *Reg Anaesth* 10:175-183, 1985
37. Hall DG: Serum magnesium in pregnancy. *Obstet Gynecol* 9:158-162, 1957
38. Newman RL: Serum electrolytes in pregnancy, parturition, and puerperium. *Obstet Gynecol* 10:51-57, 1957