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

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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 μg/kg bolus and 5 $\mu g \cdot kg^{-1} h^{-1}$) and pancuronium (0.15 mg/kg bolus and 0.05 $mg \cdot kg^{-1} h^{-1}$) provided paralysis. Two hours after the thiopental bolus, all animals received an intravenous (iv) infusion of bupivacaine (1 $mg \cdot kg^{-1} min^{-1}$). The control group (5 animals) received bupivacaine only. The Mg^{++} group (5 animals) received $MgSO_4$ 140 mg/kg iv and 80 $mg \cdot kg^{-1} h^{-1}$ 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 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 (QTI_c) 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 ± 2.3 (SEM) mg/kg in the control group and 13.9 ± 2.5 mg/kg in the Mg^{++} group. This corresponded to plasma bupivacaine concentrations of 12.2 ± 1.8 μg/ml and 12.8 ± 1.4 μg/ml in the control and Mg^{++} groups, respectively. Serious cardiac dysrhythmias occurred at an average bupivacaine dose of 9.5 ± 1.7 mg/kg in the control group but did not occur at all in four of five animals in the 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.[1] A large number of patients with preeclampsia also receive regional analgesia for cesarean delivery or attenuation of labor pain.[2,3] 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.[4] Avoidance of the use of bupivacaine has been advocated.[5]

The effect of magnesium administration on the CNS and cardiovascular toxicity of bupivacaine has not been studied. Because of its anticonvulsant properties,[6] 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,[7–9] 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).[10,11] Magnesium has been shown to be an effective antidysrhythmic in a variety of cases of QTI prolongation and TdP.[12–15] 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 normocarbia, and if needed, sodium bicarbonate was administered to obtain a *p*H 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 μq/kg iv) was administered followed by a 5 $\mu g \cdot kg^{-1} h^{-1}$ maintenance infusion. All animals were paralyzed with pancuronium (0.15 mg/kg iv with infusion of 0.05 $mg \cdot kg^{-1} h^{-1}$). A combination of low-dose fentanyl with pancuronium has been shown to have minimal effects on the cardiac conduction system in the dog.[16]

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 $mg \cdot kg^{-1} min^{-1}$ starting 2 h after the thiopental bolus. The control group received

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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 mg·kg^{-1} 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-μl injection. Bupivacaine standard concentrations of 2.5–40.0 μg/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° 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 ± 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 ± 0.03 mM (1.3 ± 0.06 mEq/l) to a mean of 2.42 ± 0.18 mM (4.8 ± 0.36 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 ± 2.3 mg/kg in the control group and 13.9 ± 2.5 mg/kg in the Mg^{++} group (fig. 2). This corresponded to plasma bupivacaine concentrations of 12.2 ± 1.8 μg/ml and 12.8 ± 1.4 μg/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^{++} (before $MgSO_4$)	145 ± 12		
	Mg^{++} (after $MgSO_4$)	150 ± 8	144 ± 6	133 ± 7†‡
MAP (mmHg)	Control	135 ± 9	140 ± 8	138 ± 13
	Mg^{++} (before $MgSO_4$)	121 ± 5		
	Mg^{++} (after $MgSO_4$)	127 ± 5†	132 ± 7	131 ± 8
PCWP (mmHg)	Control	6.0 ± 0.5	9.4 ± 0.08*	12.8 ± 0.5*‡
	Mg^{++} (before $MgSO_4$)	5.0 ± 0.03		
	Mg^{++} (after $MgSO_4$)	5.0 ± 0.8	10.0 ± 2.0*	13.4 ± 2.3*†‡
LVSWI (g M/m^2/beat)	Control	58.9 ± 9.3	51.2 ± 7.8	44.4 ± 8.7*‡
	Mg^{++} (before $MgSO_4$)	66.4 ± 4.7		
	Mg^{++} (after $MgSO_4$)	61.9 ± 6.1	55.2 ± 4.6*	51.0 ± 5.0*
Serum Mg^{++} (mM)	Control	0.67 ± 0.03	—	—
	Mg^{++} (before $MgSO_4$)	0.67 ± 0.04	—	—
	Mg^{++} (after $MgSO_4$)	2.42 ± 0.18†	—	—
Ionized serum Ca^{++} (mM)	Control	1.03 ± 0.14	—	—
	Mg^{++} (before $MgSO_4$)	1.14 ± 0.13	—	—
	Mg^{++} (after $MgSO_4$)	1.09 ± 0.13	—	—
Serum K^+ (mEq/l)	Control	2.68 ± 0.04	—	—
	Mg^{++} (before $MgSO_4$)	2.68 ± 0.11	—	—
	Mg^{++} (after $MgSO_4$)	2.52 ± 0.11	—	—

Values are mean ± SEM. $P < 0.05$.
* Different from baseline.
† Different from Mg^{++} (before $MgSO_4$).
‡ 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^{++} 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^{++} 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^{++} 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^{++} 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^{++} 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 $MgSO_4$ bolus and infusion mimic the recommended magnesium levels for treatment of preeclampsia.[17]

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_{max} of the cardiac action potential[7,18,19] and subsequent slowed conduction creates conditions that allow the occurrence of unidirectional block and reentry, leading to ventricular ectopy.[5,20] Slowing of cardiac conduction by bupivacaine has been demonstrated in various intact animal and isolated heart preparations.[7,9,10,21] 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 QTI_c 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

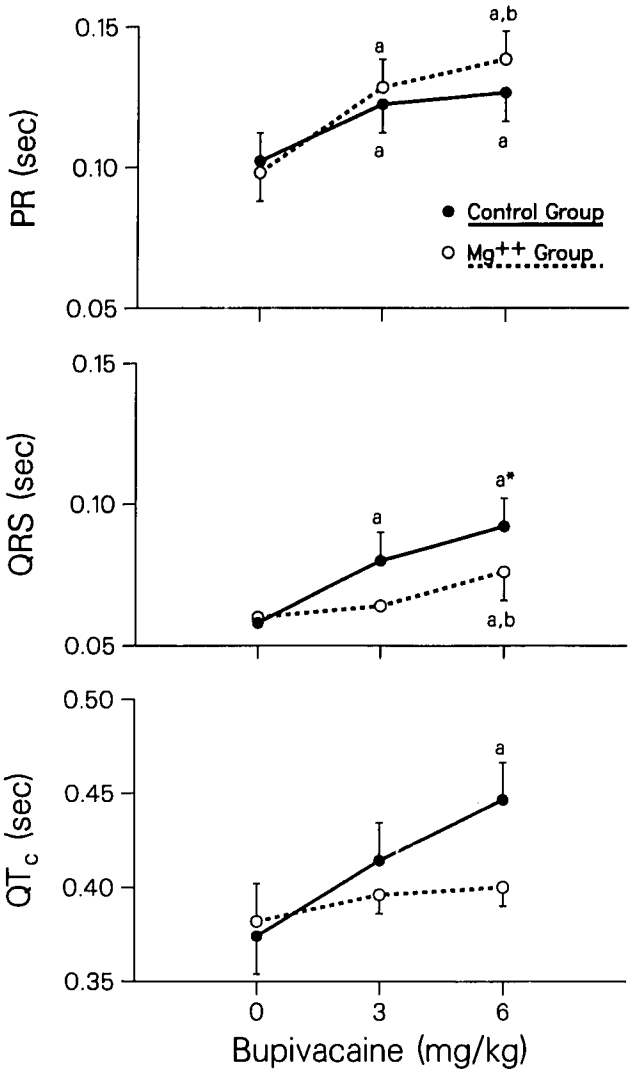

FIG. 1. The effect of bupivacaine infusion on the PR, QRS, and QT_c intervals of the ECG. a = different from 0 mg/kg; b = different from 3 mg/kg. *Difference between control and Mg^{++} groups. $P < 0.05$.

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[21,22]). 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.[22] Magnesium may lessen the effect of bupivacaine on the slowing of cardiac conduction by making the resting membrane potential more negative,[23] by increasing V_{max},[24,25] or by shortening cardiac action potential duration.[24,26,27]

Perhaps the most important effect of bupivacaine on induction of cardiac dysrhythmias is QTI prolongation and increased temporal dispersion of the effective refractory period.[28] As with other conditions associated with a prolonged QTI, this can lead to TdP.[11-15]

Prior magnesium administration in the Mg^{++} group prevented the QTI prolongation caused by bupivacaine, which the control group experienced. By preventing prolongation of the QTI, magnesium may lessen the dispersion of QTI 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.[12]

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[27] and might enhance the myocardial depression caused by bupivacaine, which may also have calcium channel-blocking properties.[29,30]

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

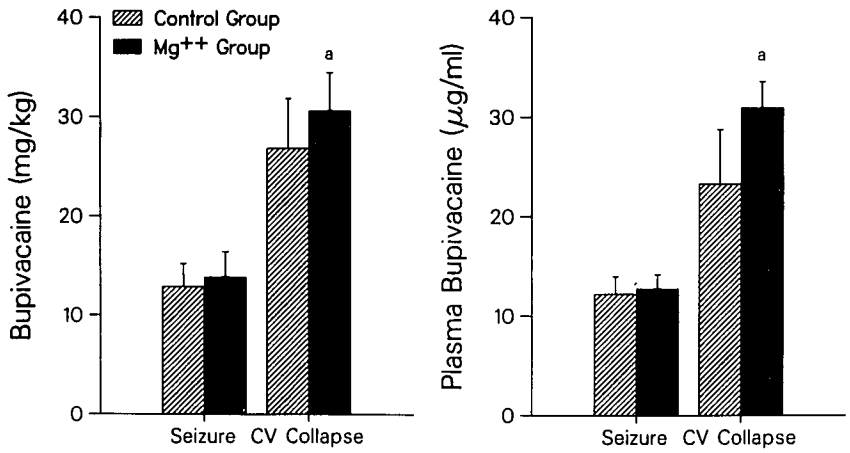

FIG. 2. The iv dose (mg/kg) and plasma concentrations (μg/ml) of bupivacaine causing seizure and cardiovascular collapse in the two groups. a = different from seizure. $P < 0.05$.

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^{++} 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^{++} 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^{++} 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,[31,32] and may be related to a higher adrenergic tone in our lightly anesthetized dogs.

Only in the Mg^{++} 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,[33] there is some question whether magnesium has a central anticonvulsant effect.[34] Because magnesium increases cerebral blood flow,[17] our findings may be explained by an increased transport of bupivacaine to cerebral tissue, which overcame any anticonvulsant effects of Mg^{++}. The dose of bupivacaine that caused seizures in our animals was significantly higher than that found by Avery *et al.*[32] (5.1 mg/kg in dogs anesthetized with morphine and N_2O), Liu *et al.*[35] (5.0 mg/kg in awake dogs), and Sage *et al.*[36] (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.[37,38] Like bupivacaine overdose, hypomagnesemia is associated with QTI prolongation and TdP ventricular tachycardia.[13,15] 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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