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Lipid Emulsion Infusion Rescues Dogs From Bupivacaine-Induced Cardiac Toxicity

Guy Weinberg, M.D., Richard Ripper, B.A., Douglas L. Feinstein, Ph.D., and William Hoffman, Ph.D.

Background and Objectives: We previously demonstrated in rats that intravenous infusion of a lipid emulsion increases survival in resuscitation from severe bupivacaine cardiac toxicity. The present studies were undertaken to determine if this method is similarly effective in a non-rodent model using a larger animal.

Methods: Bupivacaine, 10 mg/kg, was administered intravenously over 10 seconds to fasted dogs under isoflurane general anesthesia. Resuscitation included 10 minutes of internal cardiac massage followed with either saline or 20% lipid infusion, administered as a 4-mL/kg bolus followed by continuous infusion at 0.5 mL/kg/min for 10 minutes. Electrocardiogram (EKG), arterial blood pressure (BP), and myocardial pH (pHm) and pO2 (pmO2) were continuously measured.

Results: Survival after 10 minutes of unsuccessful cardiac massage was successful for all lipid-treated dogs (n = 6), but with no survivors in the saline controls (n = 6) ($P < .01$). Hemodynamics, PmO2, and pHm were improved during resuscitation with lipid compared with saline treatment in which dogs did not recover.

Conclusions: We found that infusing a lipid emulsion during resuscitation from bupivacaine-induced cardiac toxicity substantially improved hemodynamics, pmO2, and pHm and increased survival in dogs. *Reg Anesth Pain Med 2003;28:198-202.*

Key Words: Bupivacaine, Lipid emulsion, Cardiotoxicity, Local anesthesia, Resuscitation.

Bupivacaine overdose can lead to fatal cardiac toxicity in the form of severe arrhythmias and contractile dysfunction.[1,2] We have previously shown that an intravenous infusion of a lipid emulsion attenuates the adverse hemodynamic effects of bupivacaine.[3] In that study, pretreatment of rats with a lipid emulsion increased both the bupivacaine dose and serum concentration required to produce asystole compared with those in corresponding controls. We also showed that animals resuscitated from bupivacaine overdose with a lipid infusion had greater survival rates than controls. We found that infusing the emulsion during resuscitation increased the LD50 for a rapid (10 second) bolus of bupivacaine by 50%.

In addition to the rat, it is important to demonstrate that bupivacaine toxicity can be treated with lipid emulsion in other species closer in size to man and to determine how each treatment may affect myocardial metabolism. In this study, we evaluated the effect of lipid infusion or sham saline treatment on hemodynamics and survival following bupivacaine toxicity in dogs. Myocardial tissue oxygen pressure (pmO2) and pH (pHm) were measured during each treatment as a way to evaluate local changes in myocardial metabolism. We hypothesized that lipid infusion following bupivacaine treatment would improve recovery of cardiac function, hemodynamics, and myocardial metabolism compared with saline-treated controls.

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From the Department of Anesthesiology, University of Illinois at Chicago College of Medicine (G.W., D.L.F., W.H.), Chicago, Illinois; and the Veterinary Medical Unit, Chicago VA Hospital Westside Division (R.R.), Chicago, Illinois.

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Reprint requests: Guy Weinberg, M.D., Department of Anesthesiology, M/C 515, University of Illinois at Chicago, 1740 West Taylor St, Chicago, IL 60612. E-mail guyw@uic.edu

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Methods

This study was approved by the Institutional Animal Care Committee, and experiments were per-

formed at the Veterans Administration Chicago Healthcare System, West Side Division Animal Research Facility. Non-purpose bred male hounds (22 to 26 kg) were used in this study. Dogs were fasted overnight. Investigators were not blinded to the treatment schedule.

A Paratrend tissue probe (Codman, Newark, NJ) was calibrated on the day of the study using precision gases. The probe is 0.5 mm in diameter, with 2 sensors measuring PmO2 and pHm contained in the final 2 cm. The void surrounding the pHm sensor is filled with acrylamide gel containing phenol red. Changes in hydrogen ion concentration produce color changes in phenol red, which can be detected by the pH fiber optic sensor. A fluorescence method is used to measure the partial pressure of dissolved or gaseous oxygen for the fiber optic pmO2 sensor. The 0% to 90% response times for the pmO2 and pHm sensors were 78 seconds and 70 seconds, respectively.

On the day of the study, the dog was anesthetized with 5 mg/kg propofol, intubated, and ventilated with 1.5% isoflurane and 30% oxygen. Catheters were inserted into the femoral artery for blood pressure (BP) recording and blood gas sampling, and the femoral vein for fluid and drug administration. Sterile saline was infused intravenously (4 mL $\cdot$ $kg^{-1} \cdot hr^{-1}$) for fluid maintenance. The left ventricle was exposed through a left 5th intercostal space incision. The Paratrend probe was inserted into the myocardium in the region between the first and second diagonal branch of the left anterior descending coronary artery, parallel to the surface of the heart 6 mm below the surface using an 18-gauge angiocatheter as an introducer. Mechanical ventilation was adjusted to maintain arterial pCO2 at 35 $\pm$ 2 mm Hg, and inspired oxygen concentration was maintained at 30% with the balance nitrogen. Body temperature was maintained at 38°C using a warming pad.

After equilibration of the myocardial tissue probe for 45 minutes, baseline measures of mean arterial pressure (MAP), heart rate, pmO2, and pHm were recorded, and an arterial blood gas sample was measured. Each dog received an intravenous infusion of 10 mg/kg bupivacaine over 10 seconds. The time was noted at the onset of criteria for circulatory arrest (heart rate [HR] $<$10 and mean BP below 30 mm Hg), at which time internal cardiac massage was instituted, isoflurane was discontinued, and ventilation maintained with 100% oxygen. Internal cardiac massage alone was continued for 10 minutes, then combined with infusion of either the lipid emulsion (Intralipid 20%, Fresenius Kabi Clayton, Clayton, NC) (n = 6) or saline (n = 6), each administered as a 4-mL/kg bolus (over 2 minutes), followed by a continuous infusion of 0.5 mL $\cdot$ $kg^{-1} \cdot min^{-1}$ for 10 minutes. If sinus rhythm returned, internal cardiac massage was continued until MAP reached 30 mm Hg and 30-minute recovery measures were recorded. Dogs were killed at the end of the study using a euthanasia solution.

Statistics

Data are reported as mean $\pm$ SD. Baseline and recovery BP and HR were compared within each group using paired *t* tests. pmO2 and pHm were compared between baseline and subsequent treatments within each group using repeated measures analysis of variance with Tukey's tests for post hoc comparisons. Differences between groups for each treatment were compared by Student's *t* test. The proportion of animals surviving bupivacaine challenge in each group was compared using a z test. Statistical significance was considered as $P < .05$.

Results

In a preliminary study, 3 dogs received a lipid infusion immediately after circulatory collapse; these animals all returned to normal sinus rhythm and BP (within 10% of baseline values) in less than 5 minutes. Three dogs given the saline-based (control) resuscitation failed to develop a cardiac rhythm within 10 minutes after circulatory collapse. Based on the result of this preliminary study, we performed a study in 12 dogs (n = 6 Intralipid treatment and n = 6 saline treatment) in which the lipid or saline infusion was delayed for 10 minutes, with intervening cardiac massage, in order to produce a more clinically relevant treatment.

Under baseline conditions in the study, MAP, HR, arterial blood gases, and pH in the control and lipid-treated dogs were similar (Table 1). All 12 dogs receiving 10 mg/kg bupivacaine developed circulatory collapse (average time to criteria, 7.2 $\pm$ 2.3 minutes, n = 12). BP decreased rapidly below 30 mm Hg, while the heart continued to beat; the usual rhythm at circulatory collapse was asystole or severe bradycardia (HR $<$ 10). Only dogs treated with lipid demonstrated return of BP and HR in the recovery period.

A normal sinus rhythm was established within 5 minutes after starting the lipid infusion in all 6 dogs. Ten minutes after starting lipid infusion, myocardial function was adequate to maintain mean arterial BP above 30 mm Hg (Fig 1). Thirty minutes after administering the lipid treatment, BP and HR were close to baseline levels and the electrocardiogram (EKG) appeared normal in all dogs receiving lipid emulsion. No saline-treated dogs responded to cardiac massage or recovered sustainable hemody-

Table 1. MAP, HR, PaO2, PaCO2, and pHa Under Baseline Conditions in Saline- and Lipid-Treated Dogs

Group	No.	Treatment	MAP (mm Hg)	HR (min-1)	PaO2 (mm Hg)	PaCO2 (mm Hg)	pHa
Saline	6	Baseline	91 ± 12	122 ± 17	236 ± 69	36 ± 2	7.38 ± 0.04
		Recovery	10 ± 3*	0*			
Lipid	6	Baseline	96 ± 14	128 ± 21	228 ± 63	35 ± 2	7.39 ± 0.02
		Recovery	93 ± 12	126 ± 18	212 ± 56	36 ± 2	7.35 ± 0.04

NOTE. Data are mean ± SD.
*$P < .05$ compared with baseline.

namic parameters: none achieved a normal rhythm or BP greater than 20 mm Hg. The difference in survival between the controls and lipid-treated dogs was significant by z test, $P < .01$.

Myocardial tissue oxygen and pH are shown in Fig 2. Under baseline conditions, there was no difference between groups. Bupivacaine produced a rapid decrease in pmO2 without a change in pHm. Ten minutes after bupivacaine, pHm decreased modestly, but significantly, in both treatment groups. At the time of recovery, pmO2 and pHm returned toward baseline levels in lipid-treated dogs. At a similar time point in sham-treated dogs, pHm continued to decrease.

Discussion

We report that a lipid emulsion infusion rescues dogs from bupivacaine cardiac toxicity and improves myocardial metabolic function as evaluated by pmO2 and pHm compared with saline-treated control dogs. A 10-mg/kg bupivacaine bolus injection produced cardiovascular collapse in all dogs studied. Cardiac massage alone failed to restore cardiac activity after 10 minutes in any control dog. However, infusing a lipid emulsion plus internal

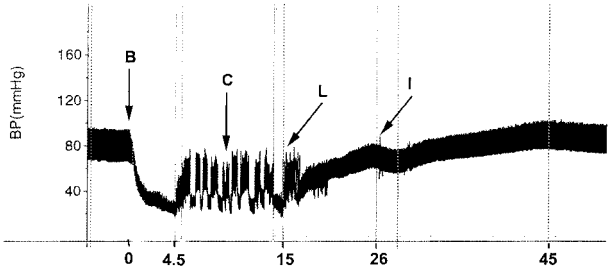

Fig 1. BP during a typical experiment. B indicates the start of a bupivacaine 10 mg/kg bolus infusion. This is taken as zero time. Criteria for circulatory collapse were reached at 4.5 minutes, and internal cardiac massage, indicated by C, was begun, causing the subsequent pressure spikes that continued until shortly after the lipid infusion, indicated by L, was begun at 15 minutes. Circulation was sufficiently established by 26 minutes (after roughly 10 minutes of lipid therapy) that isoflurane general anesthesia was restarted, indicated by I.

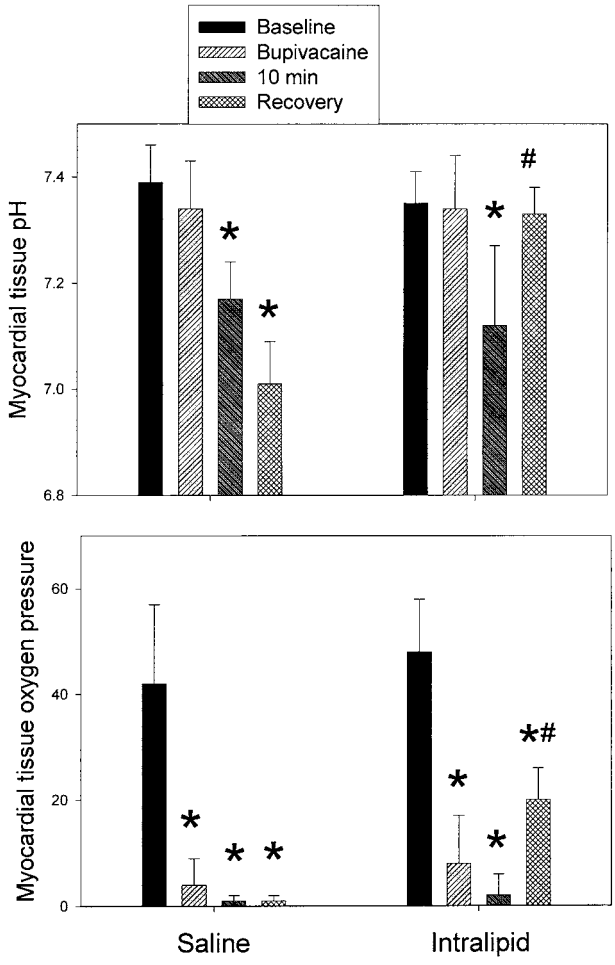

Fig 2. Myocardial tissue pH and pO2 for control (saline) and lipid-treated dogs. Internal cardiac massage was administered in both groups for 10 minutes after criteria were attained for cardiovascular collapse. Then either saline or lipid was infused to supplement the cardiac massage. Recovery values in saline-treated dogs were recorded after 10 minutes of saline treatment, without return of cardiac function in any dogs. In lipid-treated dogs, sinus rhythm returned within 5 minutes in all subjects, and recovery values were measured when mean BP returned to within 10% of baseline levels. Mean ± SD. *$P < .05$ compared with baseline for each group. #$P < .05$ compared with same treatment in saline-treated group.

cardiac massage lead to recovery of normal hemodynamics whether the treatment was initiated immediately (n = 3) or delivered after 10 minutes of circulatory arrest (n = 6). Lipid emulsion infusion may offer a novel means to treat otherwise potentially fatal bupivacaine overdose.

Previous experiments in rats in our laboratory showed a salutary effect of lipid emulsion infusion on both prevention and treatment of bupivacaine-induced cardiovascular collapse. We found irreversible cardiovascular collapse was 100% in rats receiving a bolus of 15 mg/kg bupivacaine followed by external chest compressions and saline infusion.[3] However, survival was 100% after the same bupivacaine dose among rats receiving chest compressions with a lipid emulsion infusion. The LD50 for a 10-second bupivacaine bolus was 12 mg/kg in controls and 18 mg/kg in those receiving the lipid-based resuscitation. The mechanism for this effect is unknown. One possible mechanism is that the lipid infusion creates a lipid plasma phase that essentially "extracts" the lipid soluble bupivacaine molecules from the aqueous plasma phase, making them unavailable to tissue. The partition coefficient of radiolabelled bupivacaine for a lipid phase created by mixing a lipid emulsion with plasma in vitro was 12. This suggests bupivacaine can be drawn out of the plasma aqueous phase, and therefore out of tissue. It is also possible that infused lipids can move directly into tissue and interact with bupivacaine at that level. Movement of lipid from plasma to tissue would be facilitated by plasma lipases that break triglycerides into fatty acids.[4] It is expected that individual lipemic concentrations and activity of plasma lipases could have a significant effect on bupivacaine toxicity, based on the ability to extract the local anesthetic from plasma and tissue.

We found myocardial tissue oxygen decreased to 0 mm Hg following the bupivacaine-induced asystole and recovered to normal levels after lipid treatment. The decrease in pmO2 is consistent with the loss of myocardial blood flow and oxygen delivery. Bupivacaine also uncouples oxidative phosphorylation in mitochondria, resulting in accelerated oxygen utilization without the benefit of adenosine triphosphate production.[5,6] Myocardial tissue pH decreased modestly from baseline in both groups 10 minutes after bupivacaine (Fig 2). This suggests that myocardial tissue acidosis may be attenuated after bupivacaine-induced asystole. Attenuated acidosis may enhance the heart's ability to recover from bupivacaine toxicity.

Propofol is known to suppress bupivacaine-induced seizures[7] and may be of benefit in treating bupivacaine-related cardiac depression.[8] It is commonly formulated in a 10% lipid emulsion vehicle, which theoretically could support the rationale for using this drug to treat bupivacaine toxicity, particularly before cardiac depression or severe hypotension occur. Based on a standard propofol dose of 2 mg/kg given as a bolus, the amount of lipid given would be 3% of the lipid dose given in this study. This is a much smaller amount of lipid than we have found is effective to reverse bupivacaine toxicity, but it still may be adequate to partially reverse the toxic effects of bupivacaine.[8] Further studies are necessary to determine the dose-response interaction of lipid treatment and bupivacaine toxicity.

The limitations of this study include the fact that the procedure was not blinded to the investigators. This was necessitated by different lipid and saline preparations that were visually apparent. However, each group received a similar protocol in terms of fluid infusion and cardiac massage before and during the treatment protocol. Because there was no difference in baseline or bupivacaine hemodynamic or myocardial tissue measures, we suggest that bias was not introduced by investigator awareness of the rescue protocol. The finding that all dogs recovered cardiac function within minutes of receiving a lipid infusion but no dogs recovered with saline treatment shows that reversal of bupivacaine toxicity was primarily due to intravascular infusion of the lipid emulsion.

There was a problem determining the timing of treatment for this study. In preliminary studies, we observed that rapid reversal of bupivacaine toxicity could be accomplished with lipid treatment given immediately after circulatory collapse. However, a more clinically relevant procedure that included 10 minutes of cardiac massage followed by lipid infusion was evaluated here. We suspect that an attenuated decrease in pHm after bupivacaine may be important in our ability to rescue all 6 dogs treated with lipid. We assume that modest myocardial acidosis 10 minutes after circulatory collapse may be indicative of the inhibitory effects of bupivacaine on cellular metabolic function. This may prolong the period during which lipid can be given to reverse bupivacaine toxicity.

It is a question whether 10 mg/kg bupivacaine was an excessive dose to produce toxicity in this study. A large bupivacaine dose was given in order to achieve cardiac depression rapidly and decrease the variability in the time to reach circulatory collapse. It is possible that a smaller dose of bupivacaine would have increased the number of sham-treated dogs that recovered from toxicity. Groban et al.[2] showed in a study of local anesthetic cardiac toxicity that animals surviving severe bupivacaine toxicity had much lower plasma anesthetic concen-

trations than at the onset of cardiovascular collapse. This suggests reducing bupivacaine concentration could be beneficial in treating overdose.

Our findings support further investigation of lipid-based resuscitation for treatment of bupivacaine-induced cardiac toxicity. Additional studies are required to determine the optimum dose and dosing regimen. Functional, physiologic, and histologic toxicity after rapid lipid emulsion infusion must also be studied to understand better the risks of this therapy.

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