Cardiovascular Toxicity of Local Anesthetics: An Alternative Hypothesis

Richard D. Thomas, BS, Michael M. Behbehani, PhD, Dennis E. Coyle, PhD, and Donald D. Denson, PhD

Numerous in vivo and in vitro studies have examined the etiology of reported cardiotoxicity of bupivacaine (1–8). Most recently, Clarkson and Hondeghem reported that in guinea pig ventricular muscle, both lidocaine and bupivacaine produce direct myocardial depression by blocking cardiac sodium channels (8). Bupivacaine was found to be a more potent channel blocker, which was attributed to differences in binding affinity and sodium channel association kinetics. The in vitro studies of Clarkson and Hondeghem produced signs of cardiovascular toxicity similar to those reported in vivo in sheep (3,5). Other mechanisms proposed for cardiotoxicity focus on the ability of bupivacaine to depress atrioventricular (AV) node conduction and/or myocardial contractility (4–7). However, none of the studies to date has considered the possibility of concomitant cardiovascular system (CVS) and central nervous system (CNS) toxicity, which have been reported under clinical circumstances in humans (9). These clinical observations have led to the suggestion that toxicity associated with bupivacaine is different from the toxicity ascribed to other amide local anesthetics. Whereas isolated heart experiments allow evaluation of direct myocardial effects, in vivo studies involving systemic administration do not allow independent observations of the specific isolation into the discrete contributions of the CNS and CVS to the observed toxicity. A central mechanism for the inotropic and chronotropic actions of lidocaine has been reported (10). A marked increase in the brain–blood partitioning during convulsions has also been reported for lidocaine, suggesting an increased permeability of local anesthetics across the blood–brain barrier.
blood–brain barrier during local anesthetic-induced seizures (11). Because the CNS can exert dromotropic, inotropic, and chronotropic effects on the myocardium, some of the cardiovascular system depressive effects of amino-amide local anesthetics might possibly be mediated through CNS mechanism(s) (12). If this hypothesis were true, then the apparently simultaneous onset of CNS and CVS toxicity with bupivacaine could be explained in part by extremely high brain concentrations. This study was designed to evaluate the potential contribution of the CNS to cardiac toxicity associated with amide local anesthetics by use of an in vivo model that obviates the need for systemic administration of the anesthetics.

Methods

General Procedure

Adult Sprague-Dawley rats (Charles River Laboratories) weighing 200–300 g were anesthetized with chloral hydrate (400 mg/kg). The femoral artery was cannulated for a continuous recording of blood pressure, using a blood pressure monitor 813B (CSP Inc.) and a Gould Brush 260 recorder. The animals were placed in a stereotactic instrument in the prone position. The dorsal surface of the skull was exposed, and the occipital bone was either partially or entirely excised. Figure 1 is a schematic of the primary vasomotor and cardioactive areas of the medulla. The nucleus tractus solitarius (NTS) is a primary relay station for sympathetic and parasympathetic afferent and efferent fibers of the cardiovascular system. Fibers from NTS have an inhibitory effect on the hypothalamus and on C1 cell bodies. The nucleus tractus solitarius receives excitatory signals from fibers of the carotid sinus and aortic nerve. C1 cell bodies receive inhibitory input from NTS and A1 cell bodies. Fibers from C1 cell bodies send excitatory signals to the intermediolateral column (IML) located in the cervical spinal cord (12,13). For experiments in the C1 area and the NTS an area of the occipital bone 3.0 mm wide and 2.0 mm long was excised. For injections at the IML (cervical spinal cord), the entire occipital bone was excised. Lead I electrocardiogram was continuously recorded using a Gould Brush 260 recorder.

Injections of saline caused no changes in mean arterial pressure, heart rate, PR interval, or QRS duration when injected at C1, the IML, or the NTS. In addition to positive response to chemical and electrical stimulation of correct electrode and cannula placement, anatomical verification of electrode and cannula location was required before animals were included in their experimental group. A minimum of seven animals meeting these criteria was included in each set of experiments.

The effects of local anesthetics on the fibers of the NTS and C1 (effects on cell firing rate) were studied first using bupivacaine as a model compound. A comparison between equal numbers of molecules of lidocaine and bupivacaine was then completed by injections at the NTS, C1, and the IML.

Location of C1 and the NTS

The stereotactic coordinates of C1 were 12.2–13.0 mm caudal with respect to the bregma, 0.7–1.0 mm lateral from the midline, and 7.5–8.5 mm deep with respect to the brain surface. The nucleus tractus solitarius was
located at 12.8–13.5 mm caudal, 1.0–1.5 mm lateral, and 5.5–6.5 mm deep. The C1 and NTS areas were located by stimulation with bipolar pulses, 10 V and 400 μsec, at a frequency of 10 Hz for 10 sec using a Pulsar 4bp stimulator (Frederick Haer and Co.). To confirm that only nerve cell bodies and not fibers of passage were being stimulated, L-glutamate (50 mM in 0.9% NaCl, pH 6.9) was injected into the same area. For both electrical and L-glutamate stimulations, an increase of a minimum of 10 mm Hg in mean arterial pressure indicated correct location of C1, while a decrease of at least 10 mm Hg in mean arterial pressure indicated correct location of the NTS (Fig. 2). At the conclusion of the experiment, 0.6 μl of pontamine skyblue were injected through the cannula at either the C1 area or the NTS. After a midline thoracotomy, animals were perfused with 10% formalin via the aorta. Brains were then dissected to verify electrode and/or cannula placement.

**Experiments at C1**

After proper cannula and electrode placement in the C1 area, either an equal number of molecules of 4% bupivacaine (1 μl, 1.4 μmol), or 2% lidocaine (1.6 μl, 1.4 μmol) or else 1 μl of saline was injected using a stainless steel 28-gauge hypodermic needle with a microsyringe. The effects of 4% bupivacaine (1 μl, 1.4 μmol) on the C1 cell firing rate in cells from 20 animals were measured using a 1 mm glass electrode filled with 3 M NaCl (window discriminator WDR-420, Syntronics Inc.) Arterial pressures and electrocardiogram were continuously monitored throughout these experiments.

**Experiments at the NTS**

Experiments at the NTS involved placement of a stainless steel 28 gauge hypodermic needle connected to a microsyringe. Four percent bupivacaine (1 μl, 1.4 μmol), 2% bupivacaine (1 μl, 0.7 μmol), 2% lidocaine (1.6 μl, 1.4 μM), or 4% lidocaine (0.8 μl, 1.4 μmol), or 1 μl normal saline was infused into the NTS. Effects of 4% bupivacaine (1 μl, 1.4 μmol) on the NTS cell firing rate in cells from 20 animals were measured using a 1-mm glass electrode filled with 3M NaCl (window discriminator WDR-420, Syntronics Inc.) Arterial pressures and electrocardiogram were again continuously monitored throughout these experiments.

**Statistical Analysis of the Data**

Within-animal differences in mean arterial pressure, heart rate, PR interval, and QRS duration (taken as maximum changes from control) were compared using a t-test for paired data. Intergroup comparisons were made using a one-way analysis of variance followed by the appropriate critical value test for multiple comparisons. Data are presented as means ± SD. A value of P < 0.05 was considered the minimum level of statistical significance.

**Results**

**Experiments at C1**

The activity of C1 cells in 20 animals was recorded during the application of bupivacaine (1.4 μmol). Bupivacaine increased the cell firing rate from 23.7 ± 10.5 to 45.0 ± 7.2 Hz (P < 0.01). The cell firing rates returned to control values 20 min after injection.

Application of an equal number of molecules of either bupivacaine (1.4 μmol) or lidocaine (1.4 μmol) resulted in significant decreases in mean arterial pressure (Table 1). All hemodynamic changes began within 30 sec of injection. Maximum changes occurred at 2–5 min and lasted 10–15 min after injection. Hemodynamic parameters had returned to control values by 20 min after injection. Changes in heart rate, PR interval, and QRS duration were not statistically significant.

### Table 1. Cardiovascular Effects of Bupivacaine and Lidocaine Injected at C1

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>PR interval (msec)</th>
<th>QRS duration (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine (4%, 1.4 μM)</td>
<td>-36.6 ± 7.4 †</td>
<td>-6.7 ± 6.3</td>
<td>9.7 ± 8.4</td>
<td>-1.7 ± 0.8</td>
</tr>
<tr>
<td>Lidocaine (2%, 1.4 μM)</td>
<td>-21.6 ± 1.8</td>
<td>-26.4 ± 20.3</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

†Mean change from control ± SD.

![](image-url)
Table 2. Cardiovascular Effects of Bupivacaine and Lidocaine Injected at the IML

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>PR interval (msec)</th>
<th>QRS duration (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine (4%, 1.4 µmol)</td>
<td>-43.4 ± 10.6 µl</td>
<td>-50.3 ± 13.8 µl</td>
<td>1.7 ± 1.7</td>
<td>1.1 ± 1.0</td>
</tr>
<tr>
<td>Lidocaine (4%, 1.4 µmol)</td>
<td>-13.9 ± 5.0 µl</td>
<td>-25.5 ± 7.7 µl</td>
<td>0.5 ± 1.2</td>
<td>1.5 ± 3.2</td>
</tr>
</tbody>
</table>

*Mean change from control ± sd.

P < 0.01.

P < 0.05.

P < 0.025.

Table 3. Cardiovascular Effects of Bupivacaine and Lidocaine Injected at the NTS

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>PR interval (msec)</th>
<th>QRS duration (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine (2%, 0.7 µmol)</td>
<td>-27.1 ± 8.6 µl</td>
<td>-50.6 ± 22.0 µl</td>
<td>11.6 ± 5.6</td>
<td>4.5 ± 3.4</td>
</tr>
<tr>
<td>Bupivacaine (4%, 1.4 µmol)</td>
<td>-25.6 ± 6.8 µl</td>
<td>-85.1 ± 48.0 µl</td>
<td>5.6 ± 4.2</td>
<td>16.7 ± 8.0</td>
</tr>
<tr>
<td>Lidocaine (2%, 1.4 µmol)</td>
<td>-12.5 ± 5.7 µl</td>
<td>-37.9 ± 19.3 µl</td>
<td>9.2 ± 6.2</td>
<td>2.0 ± 1.9</td>
</tr>
<tr>
<td>Lidocaine (4%, 1.4 µmol)</td>
<td>-8.0 ± 3.1 µl</td>
<td>-3.2 ± 7.8</td>
<td>1.09 ± 2.04</td>
<td>5.8 ± 3.2</td>
</tr>
</tbody>
</table>

*Mean change from control ± sd.

P < 0.025.

P < 0.05.

Experiments at the IML

Application of an equal number of molecules of either bupivacaine or lidocaine (1.4 µmol) significantly decreased both mean arterial pressure and heart rate (Table 2). All hemodynamic changes began within 30 sec of injection. Maximum changes occurred at 2-5 min and lasted 10-15 min after injection. Hemodynamic parameters had returned to control values by 20 min after injection. No statistically significant electrocardiographic changes were noted for either bupivacaine or lidocaine.

Experiments at the NTS

The activity of NTS cells in 20 animals was recorded during the application of bupivacaine (1.4 µmol). Bupivacaine caused a decrease in the cell firing rate from 38.1 ± 10.6 to 17.6 ± 7.7 Hz (P < 0.01). The cell firing rates returned to control values within 20 min. Application of 1.4 µM of bupivacaine produced significant decreases in both mean arterial pressure and heart rate (Table 3). All hemodynamic changes began within 30 sec of injection. Maximum changes noted at 2-5 min lasted for 10-15 minutes after injection. Hemodynamic parameters had returned to control values within 20 min after injection. Electrocardiographic changes were noted within the first 5 min after injection. However, arrhythmias developed and worsened 15-20 min after injection. Prolongation of the PR interval and QRS duration were noted in many animals, but the increases were not statistically significant. Injection of 0.7 µM of bupivacaine in a volume identical to the previous experiments with 1.4 µmol of bupivacaine produced identical changes. Injection of 2% lidocaine (1.4 µmol) resulted in changes in mean arterial pressure, heart rate, PR interval, and QRS duration statistically similar to those described for both bupivacaine treatments, although the magnitude of the effects tended to be less severe. Injection of 1.4 µmol of lidocaine in one-half the volume, as described in the first series of lidocaine experiments, decreased mean arterial pressure, heart rate, and increases in PR interval and QRS duration. However, in this series, only the decrease in mean arterial pressure was statistically significant.

Ventricular Arrhythmias with Local Anesthetics Applied at C1, the IML, and the NTS

Application of an equal number of molecules (1.4 µmol) of either bupivacaine or lidocaine at the C1 area of the medulla resulted in no ventricular arrhythmias. Application of an equal number of molecules (1.4 µmol) of either bupivacaine or lidocaine at the IML was associated with ventricular arrhythmias in 14.3% of the animals in each group. Application of both 4% bupivacaine and 4% lidocaine in equimolar amounts (1.4 µmol) at the NTS produced ventricular arrhythmias in 55% of the animals in each group. When 2% bupivacaine (0.7 µmol) was applied to the NTS, ventricular arrhythmias occurred on 38% of the animals. When 2% lidocaine (1.4 µmol) was applied to the NTS, 36% of the animals developed ventricular arrhythmias. Figure 2 A and B chronologically sum-
Table 4. Frequency of Ventricular Arrhythmias Produced by Injection of Bupivacaine or Lidocaine at C1, the IML, or the NTS

<table>
<thead>
<tr>
<th>Area</th>
<th>Bupivacaine (2%, 0.7 µmol)</th>
<th>Bupivacaine (4%, 1.4 µmol)</th>
<th>Lidocaine (2%, 1.4 µmol)</th>
<th>Lidocaine (4%, 1.4 µmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>—</td>
<td>0/8</td>
<td>0/8</td>
<td>—</td>
</tr>
<tr>
<td>IML</td>
<td>1/7</td>
<td>1/7</td>
<td>1/7</td>
<td>—</td>
</tr>
<tr>
<td>NTS</td>
<td>3/8</td>
<td>6/11</td>
<td>4/11</td>
<td>6/11</td>
</tr>
</tbody>
</table>

*Frequency; minimum n = 7.

summarizes the development of ventricular arrhythmias with 4% bupivacaine (1.4 µmol) and 2% lidocaine (1.4 µmol) placed at the NTS. In all animals in which 2% lidocaine, 4% lidocaine, and 2% bupivacaine were used, normal sinus rhythm returned within 30 min without treatment. When 4% bupivacaine was used, 50% of the animals developing ventricular arrhythmias returned to normal sinus rhythm within 30 min without treatment, whereas the ventricular arrhythmias were fatal in the other 50%.

In all cases, the onset of ventricular arrhythmias occurred between 5 and 15 min after application of either lidocaine or bupivacaine and reached maximum severity at 15 min. The frequency of occurrence of ventricular arrhythmias after injection of bupivacaine or lidocaine at C1, the IML, and the NTS are presented in Table 4.

Discussion

Chloral hydrate was selected as the anesthetic agent used in this study because it produces fewer alterations in normal CNS function than other commonly used anesthetics (14). The seemingly large amounts of bupivacaine and lidocaine used in the present study represent approximately 20% of the total amount expected in the brain of a rat under conditions producing cardiovascular system toxicity. This value was estimated using the blood–brain partitioning coefficient of 4.5 reported for lidocaine (11), a brain volume of 1.2 ml for a 250-g Sprague Dawley rat (15), and an end-injection arterial blood concentration of 70 µg/ml (Denson et al., unpublished results). These amounts were chosen for a maximum likelihood that slow diffusion in the presence of rapid systemic absorption would still allow blockage of enough fibers so that dromotropic, inotropic, and/or chronotropic effects could be detected. Two and four percent solutions were chosen so that the selected amounts of drug could be introduced in a volume small enough to maximize the exposure of only the desired region.

Results obtained in the C1 area suggest that the major action of both lidocaine and bupivacaine is on axons of the nerve cells rather than on cell bodies. If the drugs acted primarily on the C1 cell bodies, then application of local anesthetic to this region would have resulted in a decrease rather than an increase in cell firing rate. The observed increase in cell firing rate is consistent with the fact that all input to the C1 cell bodies is inhibitory in the resting state (Fig. 1). Thus blockade of these fibers would remove the inhibitory input, resulting in an increase in cell firing rate. The return of cell firing rate to control by 20 min after injection is consistent with the return of blood pressure to control values at 20 min after injection. The observation of hypotension without bradycardia or ventricular arrhythmias supports the hypothesis that in the resting state, the C1 region has a tonic excitatory influence on the spinal cord neurons that are involved in maintenance of arterial blood pressure. A comparison of equal numbers of bupivacaine and lidocaine molecules demonstrated that bupivacaine produced a more pronounced decrease in mean arterial pressure.

This hypothesis is further substantiated by the experiments at the IML, which resulted in the same decrease in mean arterial pressure as did similar experiments at C1. However, decreases in mean arterial pressure when either bupivacaine or lidocaine were applied at the IML were accompanied by significant decreases in heart rate. These results are in good agreement with clinical observations regarding high spinal anesthesia and again show a discrimination between bupivacaine and lidocaine, bupivacaine causing a more profound effect on both mean arterial pressure and heart rate.

Injections at the NTS produced several changes. The primary action of both bupivacaine and lidocaine at the NTS also appears to be on fibers rather than on cell bodies. This hypothesis is supported by the fact that local anesthetics resulted in a significant decrease in cell firing rate when applied to the NTS. The nucleus tractus solitarius receives only excitatory input fibers, and thus blockade of these fibers would be expected to result in a decrease in cell firing rate (Fig. 1). In addition to significant changes in blood pressure and heart rate, prolongation of the PR interval and QRS duration was observed in most animals. Bupivacaine appeared to be at least twice as potent as lidocaine in producing these changes. The nucleus tractus solitarius appears to be the most sensitive area of the three studied, in terms of chronotropic and dromotropic effects on the heart.

At each region, adverse effects on heart rate and blood pressure were noted almost immediately. However, maximum electrocardiographic effects were noted at 15 min. Diffusion coefficients calculated for bupivacaine and lidocaine are similar and suggest that 16
min are required for either drug to diffuse 1 mm³ in biologic tissue. The time delay in arrhythmia development may be due to slow diffusion, with subsequent block of enough fibers to produce observable changes. Such a delay would not be expected after systemic administration because a uniform delivery of drug to these regions would be achieved by cerebral capillary blood flow.

The incidence of ventricular arrhythmias was similar when either bupivacaine or lidocaine were applied to the IML. Both local anesthetics produced arrhythmias with the same frequency when applied to the NTS. Although the incidence of ventricular arrhythmias was similar for both lidocaine and bupivacaine, it is important to understand that the qualitative aspects of the arrhythmias were very different for lidocaine and bupivacaine (Fig. 3). This difference is clearly illustrated by the fact that all lidocaine-induced arrhythmias spontaneously resolved, whereas 50% of the arrhythmias produced by bupivacaine proved fatal. No arrhythmias were recorded when either drug was applied in the C1 region. A combination of hypotension and bradycardia might possibly precipitate the ventricular arrhythmias noted in the present study. However, the time course of hypotension and bradycardia do not support this hypothesis because heart rate and to a greater extent blood pressure have nearly returned to control values by 15 min. These data suggest that local anesthetics have a direct dromotropic effect, particularly when placed at the NTS.

The observation that all animals that developed ventricular arrhythmias after lidocaine application reverted spontaneously to normal sinus rhythm whereas approximately 50% of the bupivacaine group did not, suggests that the "fast on-slow off" mechanism proposed by Clarkson and Hondeghem to explain differences in direct myocardial depressant effects of lidocaine and bupivacaine may also be operative within the CNS (8). In addition, lidocaine (and perhaps bupivacaine) may exhibit differential effects depending on the dose. Clearly, dose–response data are required to fully understand the present results.

Now that we have verified our hypothesis that chronotropic and dromotropic (and perhaps inotropic) changes can be produced by high concentrations of both bupivacaine and lidocaine in various medullary regions, the following question arises; can such effects occur in clinical practice? Simon et al. recently reported that uptake of lidocaine into the brain from blood increased by a factor of four during a convulsion (11). However, the original hypothesis of Simon et al. that the decreases in pH associated with convulsions resulted in increased uptake and increased intracellular "trapping" of lidocaine, has been refuted by Pardridge et al., who demonstrated a decrease in uptake of lidocaine by the brain with decreases in pH (16). These observations suggest there are alterations in the permeability of the blood–brain barrier resulting in increased drug extraction during convulsions. Other studies by Pardridge et al. demonstrated that lidocaine transport across the blood–brain barrier is independent of a ɑ₁-acid glycoprotein concentration (17). Thus lidocaine does not obey the free drug hypothesis, which states that only free (unbound) drug is available for transport across the blood–brain barrier. Because ɑ₁-acid glycoprotein is the predominant plasma protein for binding both lidocaine and bupivacaine at concentrations <10 μg/ml, we are conducting similar studies designed to elucidate the characteristics of movement of bupivacaine across the blood–brain barrier (18). The above observations suggest that abnormally high brain concentrations could accompany convulsions produced by local anesthetics resulting in adverse cardiovascular system effects.

The observations in the present study, which show...
the same incidence of arrhythmias with bupivacaine and lidocaine, could differ from clinical observations because the antiarrhythmic effect of lidocaine may counteract the CNS arrhythmic effect when lidocaine is given systemically. In the clinical setting, the magnitude of the CNS effects on the cardiovascular system will be governed by the physicochemical properties of the drug in question that dictate uptake of drugs into the CNS entry and accumulation. Accumulation of high concentrations of bupivacaine in the brain during convulsions could explain the apparently simultaneous onset of CNS and CVS toxicity. Moreover, the site(s) and mechanism(s) of action within the CNS appear to be identical for bupivacaine and lidocaine. Thus bupivacaine does not appear to be an "aberrant" local anesthetic structure as some have suggested, but rather produces more profound effects related to potency and physicochemical properties.

In conclusion, our data demonstrate direct application of local anesthetics within the medullary regions of the CNS can result in hypotension, bradycardia, and ventricular arrhythmias similar to those reported in humans after accidental intravenous injections of both bupivacaine and lidocaine (9,19). The fact that profound cardiovascular toxicity is observed clinically with bupivacaine but rarely with lidocaine argues that differences in physicochemical properties and blood-brain barrier transport characteristics do not allow sufficiently high concentrations of lidocaine to enter the cardioactive areas of the CNS. These data strongly suggest that CNS plays a role in mediation of the CVS toxicity of local anesthetics and demonstrate the need to consider both central nervous system and direct myocardial depressive properties when evaluating local anesthetic toxicity.

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References