Amrinone Is Superior to Epinephrine in Reversing Bupivacaine-induced Cardiovascular Depression in Sevoflurane-anesthetized Dogs

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Background: Bupivacaine-induced cardiovascular depression is known to be difficult to treat, and the efficacy of epinephrine for treatment of bupivacaine-induced cardiovascular depression is in doubt. We compared the efficacy of amrinone with that of epinephrine for the treatment of bupivacaine-induced cardiovascular depression in anesthetized dogs.

Methods: In dogs receiving 1.5–2% sevoflurane anesthesia, 0.5% bupivacaine was infused at a rate of 0.5 mg·kg⁻¹·min⁻¹ intravenously until mean arterial blood pressure decreased to 40 mmHg or less. In the amrinone group (n = 9), amrinone (4 mg·kg⁻¹ intravenously) was given immediately after cardiovascular depression, followed by intravenous infusion at a rate of 0.1 mg·kg⁻¹·min⁻¹. In the epinephrine group (n = 9), epinephrine (0.01 mg·kg⁻¹, intravenously) was given as a bolus, and the same dose was given again as required.

Results: All nine dogs that received amrinone survived. Of the nine dogs that received epinephrine, five survived; fatal cardiovascular depression developed in the four remaining animals (P < 0.05). Only one animal in the amrinone group showed tachyphylaxis with wide QRS complexes during resuscitation, whereas all nine animals in the epinephrine group showed tachyphylaxis with wide QRS complexes during resuscitation.


ACCIDENTAL intravenous injection of bupivacaine may produce profound cardiovascular depression, from which successful resuscitation may be difficult.¹ In clinical settings²⁻⁵ and laboratory investigations,⁶⁻¹³ epinephrine has commonly been used to treat bupivacaine-induced cardiovascular depression. However, the use of epinephrine to treat bupivacaine-induced cardiovascular depression remains controversial.⁷⁻⁸

Amrinone, a new inotropic agent, increases intracellular cyclic adenosine monophosphate and Ca²⁺ through the inhibition of phosphodiesterase fraction III. This drug has been reported to be effective for profound cardiovascular depression in situations in which sympathomimetic agents are ineffective.⁹ It has been found that amrinone can reverse bupivacaine cardiotoxicity in pigs.¹⁰ The current study was performed to compare the efficacy of amrinone with that of epinephrine for the treatment of bupivacaine-induced cardiovascular depression in sevoflurane-anesthetized dogs.

Materials and Methods

Animal Preparation

The study was performed in accordance with Guide for Laboratory Animals of our institution. All procedures conformed to the Guiding Principals in the Care and Use of Animals of the American Physiological Society.

Eighteen mongrel dogs of either sex (body weight 8–16 kg) were studied. Anesthesia was induced with ketamine (2 mg·kg⁻¹, intravenously) and maintained with 2–3% sevoflurane in O₂ during surgical preparation. The trachea was intubated after administration of succinylcholine (1 mg·kg⁻¹, intravenously), and the lungs were ventilated with a volume-controlled respirator (R-60, Aika, Tokyo, Japan). Lactated Ringer's solution was infused at a rate...
of 5 ml·kg⁻¹·h⁻¹ throughout the study. Heart rate was continuously monitored from lead II of the electrocardiograph. A high-fidelity transducer-tipped catheter (7-French, 435326, Toyota Instruments, Tokyo, Japan) was placed in the descending aorta via the left femoral artery to monitor systolic and diastolic arterial blood pressures and mean arterial blood pressure (MAP). A polyethylene catheter placed in the left axillary artery was used to obtain blood samples. A second polyethylene catheter was inserted into the superior vena cava via the left axillary vein to measure central venous pressure. A balloon-tipped catheter (7-French, Swan-Ganz, American Edwards Laboratories, Irvine, CA) was introduced into the pulmonary artery via the right external jugular vein, and cardiac output was measured by the thermodilution method. A high-fidelity transducer-tipped catheter (Micro-Tip catheter pressure transducer, 8-French, PC380, Millar Instruments, Houston, TX) was placed in the left ventricular cavity via the right internal carotid artery to measure left ventricular pressure. The rate of increase in left ventricular pressure (left ventricular dP/dt) was obtained with an analogue-differentiating circuit incorporating an analogue–digital converter (Contractility Unit 1323, NEC San-ei Instruments, Tokyo, Japan). Hemodynamic variables were continuously monitored with a polygraph (Recti-Hortiz-8K23, NEC San-ei Instruments). Left ventricular pressure, left ventricular dP/dt, left ventricular end-diastolic pressure, and electrocardiographic signals were also fed to another recorder (Visigraph 5L37, NEC San-ei Instruments). These four parameters were recorded on a multichannel photographic oscillograph at a paper speed of 50 cm·s⁻¹ to determine the time constant of isovolumic pressure decrease after the attainment of maximum negative left ventricular dP/dt.¹¹

After surgical preparation, the dogs were allowed to breathe 1.5–2% sevoflurane in O₂ spontaneously to stabilize hemodynamics for 30 min before the start of experiments. If movement was observed with use of 1.5% sevoflurane anesthesia, the concentration of sevoflurane was increased.

**Experimental Design**

The dogs were randomly assigned to receive either amrinone or epinephrine. After baseline recordings were obtained, 0.5% bupivacaine (Marclain, Fujisawa Pharmaceuticals, Tokyo, Japan) was administered at a rate of 0.5 mg·kg⁻¹·min⁻¹ through the peripheral venous catheter. Bupivacaine was continuously infused and sevoflurane was inhaled until MAP decreased to 40 mmHg or less, which was defined as the point of cardiovascular depression in this study. After respiratory arrest, which occurred about 10 min before cardiovascular depression, the lungs were mechanically ventilated. When MAP had decreased to 40 mmHg or less, the amrinone group received amrinone (Caltonic, Yamamouchi Pharmaceuticals, Tokyo, Japan) as a bolus of 4 mg·kg⁻¹ followed by infusion at a rate of 0.1 mg·kg⁻¹·min⁻¹ through the central venous catheter.

This dose used and administrative method were based on the report by Lindgren et al.¹⁰ and our preliminary studies. The nine animals in the other group received epinephrine at a dose of 0.01 mg·kg⁻¹, intravenously. The same dose of epinephrine was administered repeatedly if MAP decreased to less than 40 mmHg. The dose of epinephrine and the administrative method were based on a previous report¹⁰ and our preliminary studies and also were based on the method used in clinical practice. External cardiac compression was applied while MAP remained less than 40 mmHg to circulate administrated drugs. The animals were considered to have been successfully resuscitated if MAP was maintained for more than 5 min at 60 mmHg or greater without continuous amrinone administration or additional epinephrine and if the electrocardiogram showed normal sinus rhythm and a QRS complex pattern similar to that before bupivacaine administration.

**Hemodynamic Measurement**

MAP, heart rate, left ventricular pressure, maximum left ventricular dP/dt, central venous pressure, and left ventricular end-diastolic pressure were continuously monitored. Cardiac output was measured by using iccold 5% dextrose with monitoring of the thermodilution curve, and readings were taken when a smooth thermodilution curve had been obtained twice at a 5-min interval. Values at baseline, values immediately before cardiovascular depression (before resuscitation), and values after successful resuscitation (after resuscitation) were used for analysis.

**Blood Samples for Laboratory Analysis**

Arterial blood samples for measurement of plasma bupivacaine concentration; for measurement of serum K⁺, Na⁺, and Ca²⁺ concentrations; and for blood gases were obtained at baseline and after resuscitation. Samples were assayed at the experimental unit by chromatography to measure plasma bupivacaine concentration.

**Statistical Analysis**

The chi-squared test was used to compare differences between groups. Student’s unpair t-test was used to compare differences between groups. Hemodynamic and electrolyte data were tested by ANOVA and Tukey’s test for comparison between resuscitation and for comparison between groups. Statistical significance was set at p < 0.05.

**Results**

All anesthetized dogs had normal hemodynamic response to administration of bupivacaine. A total dose of 0.5 mg·kg⁻¹ of bupivacaine infusion (0.5 mg·kg⁻¹·min⁻¹), which decreased heart rate and systolic blood pressure by 20%, was administered. After administration of bupivacaine, five survival rates were 0.01 or 0.02 mg·kg⁻¹·min⁻¹ infusion. In the remaining five dogs, resuscitation developed despite an additional 0.06–0.07 mg·kg⁻¹·min⁻¹ epinephrine, which was added to the group in survival rate (p = 0.02).

Cardiac dysrhythmias were observed, including ventricular tachycardia or fibrillation, in the group exposed to bupivacaine. The difference between the two groups was not statistically significant. Only one dog in the control group showed serious cardiac arrhythmia with wide-complex tachycardia.
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analysis were obtained at baseline and before and after resuscitation. Samples were assayed immediately after each experiment. An aliquot of arterial blood was centrifuged, and plasma was stored at –20°C. Plasma samples were assayed by high-performance liquid chromatography to measure plasma bupivacaine concentrations.

Statistical Analysis
The chi-squared test was used to identify differences between groups concerning data of survival and dysrhythmia. Student’s unpaired t test was used to identify differences between groups. Hemodynamic, blood gas, and electrolyte data were tested with paired and unpaired t tests for comparison between baseline and before resuscitation and for comparison before and after resuscitation. Statistical significance was defined as \( p < 0.05 \).

Results
All anesthetized dogs had normal sinus rhythm before the administration of bupivacaine. Intravenous bupivacaine infusion (0.5 mg·kg\(^{-1}\)·min\(^{-1}\)) caused cardiovascular depression in every animal. There were no differences in weight, sevoflurane concentration, time to cardiovascular depression, or total bupivacaine dose between groups (table 1).

Survival and Dysrhythmias
All nine dogs receiving amrinone survived. None of these animals required closed-chest cardiac massage during administration of amrinone. Of the nine dogs receiving epinephrine, five survived. These five dogs received 0.01 or 0.02 mg·kg\(^{-1}\) epinephrine during resuscitation. In the remaining four, fatal cardiovascular depression developed despite the administration of 0.05–0.07 mg·kg\(^{-1}\) epinephrine. The difference between the groups in survival rate was statistically significant (\( P = 0.02 \)).

Cardiac dysrhythmias were observed during intravenous bupivacaine infusion in three dogs in the amrinone group and in two dogs in the epinephrine group. The difference between the two groups in the incidence of dysrhythmias during bupivacaine infusion was not statistically significant. Only one animal in the amrinone group showed serious cardiac dysrhythmia, including tachyarrhythmia with wide QRS complexes and multifocal premature ventricular contractions during resuscitation with amrinone, whereas serious cardiac dysrhythmias developed in every animal in the epinephrine group (table 2 and fig. 1). The difference in the incidence of dysrhythmia during resuscitation between groups was statistically significant (\( P = 0.0001 \)).

Hemodynamic Parameters
In both groups, hemodynamic parameters were measured until the outcome of resuscitation was judged.

Intravenous infusion of bupivacaine significantly decreased MAP, heart rate, cardiac output, stroke volume, and maximum left ventricular dp/dt and significantly increased central venous pressure, left ventricular end-diastolic pressure, and the time constant of isovolumic pressure decrease after attainment of maximum negative left ventricular dp/dt. No significant differences between the two groups were found at baseline or before resuscitation. MAP, heart rate, cardiac output, and stroke volume after resuscitation were comparable between the two groups. Left ventricular end-diastolic pressure and central venous pressure remained significantly greater in the epinephrine group than in the amrinone group after resuscitation. Systemic vascular resistance significantly decreased after the administration of amrinone (table 3).

Plasma Bupivacaine Concentrations and Other Laboratory Findings
Intravenous infusion of bupivacaine resulted in similar plasma bupivacaine concentrations in the two groups (table 4). There were no statistical differences in serum K\(^+\), Na\(^+\), and Ca\(^{2+}\) concentrations between the two groups. Arterial O\(_2\) tension, CO\(_2\) tension, and pH also were comparable between the two groups at all measurement points (table 5).

Discussion
The results of this study indicate that the efficacy of amrinone is greater than that of epinephrine for the
treatment of bupivacaine-induced cardiovascular depression in sevoflurane-anesthetized dogs. First, in contrast to the high mortality rate in the epinephrine

\[
\begin{array}{ccc}
\text{A} & \text{B} & \text{C} \\
\text{ECG} & \text{ECG} & \text{ECG}
\end{array}
\]

Fig. 1. (A) Electrocardiogram (ECG) during cardiovascular depression, before treatment. (B) ECG after administration of amrinone. (C) ECG after administration of epinephrine. All animals receiving epinephrine showed this ECG pattern, and in the five surviving animals in this group the ECG spontaneously returned to sinus rhythm.

group, all the animals receiving amrinone survived \((P = 0.02)\). Second, serious ventricular dysrhythmias were rare in animals receiving amrinone compared with those receiving epinephrine \((P = 0.0001)\).

There are several limitations in study design that require discussion. First, continuous bupivacaine infusion model in this study does not completely mimic the situation of accidental intravascular injection of bupivacaine in clinical practice. In clinical practice, the cardiovascular depression occurs commonly with accidental bolus administration of bupivacaine. Accidental intravascular continuous infusion of bupivacaine, however, can occur through intravascular migration of the epidural catheter during anesthesia and pain management. During a relatively long and slow infusion of bupivacaine, the animals may benefit from compensatory mechanisms, including increased sympathetic nerve activity, increased circulating catecholamines and redistribution of blood from the very large spleen of the dogs. Second, cardiac arrest, including ventricular fibrillation, is commonly observed as part of bupivacaine-induced cardiovascular collapse in clinical practice.\(^1\)\(^4\) In this study, cardiovascular depression but not cardiac arrest was induced. Third, because the life-threatening dysrhythmias may be mediated neurologically,\(^1\)\(^2\) general anesthesia may modify the process by which cardiac arrest is induced. In addition, if amrinone or epinephrine were administered after cardiac arrest, the results are not included in the results presented. However, after cardiac arrest, the decrease in cardiac output produced by amrinone does not affect cardiac performance. Therefore, the results are not affected by the absence of amrinone treatment.
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Table 3. Hemodynamic Parameters

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<th>Amrinone Group</th>
<th>Epinephrine Group</th>
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<tr>
<td></td>
<td>Baseline (n = 9)</td>
<td>Before (n = 9)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>110 ± 6</td>
<td>46 ± 4*</td>
</tr>
<tr>
<td>HR (beats·min⁻¹)</td>
<td>117 ± 5</td>
<td>86 ± 4*</td>
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<tr>
<td>dP/dtmax (mmHg·s⁻¹)</td>
<td>2,463 ± 194</td>
<td>544 ± 98*</td>
</tr>
<tr>
<td>T (ms)</td>
<td>27 ± 2</td>
<td>57 ± 6*</td>
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<tr>
<td>CO (L·min⁻¹)</td>
<td>2.1 ± 0.2</td>
<td>0.6 ± 0.1*</td>
</tr>
<tr>
<td>SV (m·beat⁻¹)</td>
<td>18 ± 3</td>
<td>7 ± 1*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>4 ± 0.4</td>
<td>9 ± 1.3*</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>1 ± 0.6</td>
<td>7 ± 0.8*</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻⁵)</td>
<td>4,354 ± 335</td>
<td>5,729 ± 586*</td>
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</table>

Values are mean ± SEM.

Before = point immediately before cardiovascular collapse; After = point after successful resuscitation; MAP = mean arterial pressure; HR = heart rate; dP/dtmax = maximum rate of rise of left ventricular pressure; T = time constant of isovolumic pressure fall after maximum negative dP/dt; CO = cardiac output; SV = stroke volume; LVEDP = left ventricular end-diastolic pressure; CVP = central venous pressure; SVR = systemic vascular resistance.

*P < 0.05 versus baseline
†P < 0.05 versus before cardiovascular collapse.
‡P < 0.05 versus epinephrine group.

dition, if amrinone or epinephrine had been administered after cardiac arrest, the results may have been different from the results presented. During resuscitation after cardiac arrest, the decrease in systemic vascular resistance produced by amrinone may have made chest compressions ineffective to generate a reasonable MAP, during chest compressions the α-adrenergic effects of epinephrine may have produced greater coronary and brain perfusion pressures, which consequently may have provided a better outcome. Finally, methods of administration of amrinone or epinephrine for resuscitation were different and may have influenced the results in this study.

Bupivacaine-induced hemodynamic disturbances are caused mainly by depression of myocardial contractility resulting from inhibition of myocardial energetic metabolism, alterations in Ca²⁺ release from cardiac sarcoplasmic reticulum, and a decrease in the slow inward current. Amrinone, as an inhibitor of phosphodiesterase fraction III, increases intracellular cyclic adenosine monophosphate, which facilitates Ca²⁺ entry into the myocardial cells. In the current study, the significantly greater survival rate in the amrinone-treated dogs compared with the epinephrine-treated dogs may be attributable to improved myocardial contractility resulting from increased intracellular Ca²⁺. Other phosphodiesterase inhibitors, in the view of their mechanisms, may be effective for cardiovascular depression induced by bupivacaine. Therefore, further studies involving the use of other phosphodiesterase inhibitors should be performed.

Although epinephrine is reported to antagonize the cardiovascular depression induced by bupivacaine, our results demonstrated the limitation of epinephrine for treatment of bupivacaine-induced cardiovascular depression. Butterworth et al. showed that bupivacaine inhibits the production of epinephrine-induced cyclic adenosine monophosphate in vitro. This inhibition may have contributed to the limitation of epinephrine for bupivacaine-induced cardiovascular depression in the current study. Because we did not measure the serum concentration of epinephrine, it is unclear if the serum concentration of epinephrine in the current study was comparable to that in the study by Butterworth et al.

All of the dogs receiving epinephrine had severe tachyarrhythmias. In contrast, the dogs receiving amrinone did not have any dysrhythmias except for one

<table>
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<tr>
<th>Group</th>
<th>Plasma Bupivacaine (mg·ml⁻¹)</th>
<th>Values are mean ± SD.</th>
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<tr>
<td>Amrinone</td>
<td>13.6 ± 2.34</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>11.6 ± 2.67</td>
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</table>

animal that showed tachyrhythmia before cardiovascular depression. Lindgren et al.\textsuperscript{19} reported the effect of amrinone on recovery from bupivacaine-induced cardiovascular depression in pigs. In contrast to the current study, they noted serious dysrhythmias during administration of amrinone. The reason our results disagree with theirs is not clear but may be related to the difference in study design, including differences in basal anesthetic techniques, the doses of bupivacaine and amrinone, the ventilation mode, and the species. Whether antidysrhythmic drugs improved the survival rate in our epinephrine group remains doubtful, because almost all antidysrhythmic agents produce cardiovascular depression and ion-channel blockade. In animal studies, the treatment of bupivacaine-induced cardiovascular depression has been attempted with bretylium, lidocaine, and amiodarone, with varying results.\textsuperscript{5,7,18}

Various drugs can modify the hemodynamic response to bupivacaine-induced cardiotoxicity to a certain degree. In this study, a low concentration of sevoflurane was given to the dogs to prevent movement. Sevoflurane, which is a cardiodepressant agent,\textsuperscript{19} may have affected our results to some extent. In fact, the peak plasma bupivacaine concentration required to induce cardiovascular depression was less in our dogs than in those anesthetized with opioids.\textsuperscript{20,21} The ketamine used for induction of anesthesia is also thought to have had little effect on our results because the experiment was started at least 2 h after ketamine administration. There were no differences between the groups in the concentration of sevoflurane or the dose of ketamine used. Acidosis, hypoxia,\textsuperscript{22} and hyperkalemia\textsuperscript{20} may also modify the hemodynamic response to bupivacaine-induced cardiotoxicity. In this study, dogs in both groups were maintained in conditions of normocapnia, hypoxia, and normokalemia to avoid these effects.

In conclusion, sevoflurane-anaesthetized dogs, amrinone appears to be superior to epinephrine for reversal of severe cardiovascular depression induced by bupivacaine. Therefore, amrinone and other phosphodiesterase inhibitors merit further study as an initial treatment for severe cardiovascular depression after bupivacaine. However, the place of amrinone or other phosphodiesterase inhibitors in the management of cardiac arrest or life-threatening dysrhythmias caused by local anesthetic toxicity was not defined by this study.

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