Analysis of the temporal regression of the QRS widening induced by bupivacaine after intralipid administration. Study in an experimental porcine model

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KEYWORDS
Bupivacaine; Cardiac toxicity; QRS interval; Intralipid; Antidote

Abstract
Objective: The principal mechanism of cardiac toxicity of bupivacaine relates to the blockade of myocardial sodium channels, which leads to an increase in the QRS duration. Recently, experimental studies suggest that lipid emulsion is effective in reversing bupivacaine cardiac toxicity. We aimed to evaluate the temporal evolution of the QRS widening induced by bupivacaine with the administration of Intralipid.

Material and methods: Twelve pigs were anesthetized with intravenous sodium thiopental 5 mg·kg⁻¹ and sevoflurane 1 MAC (2.6%). Femoral artery and vein were canaled for invasive monitoring, analysis of blood gases and determination of bupivacaine levels. After instrumentation and monitoring, a bupivacaine bolus of 4–6 mg·kg⁻¹ was administered in order to induce a 150% increase in QRS duration (defined as the toxic point). The pigs were randomized into two groups of six individuals. Intralipid group (IL) received 1.5 mL·kg⁻¹ of IL over 1 min, followed by an infusion of 0.25 mL·kg·min⁻¹. Control group (C) received the same volume of a saline solution. The electrocardiographic parameters were recorded, and blood samples were taken after bupivacaine and 1, 5, 10 and 30 min after Intralipid/saline administration.


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Results: Bupivacaine (4.33 ± 0.81 mg/kg in IL group and 4.66 ± 1.15 mg/kg in C group) induced similar electrocardiographic changes in both groups; mean maximal percent increase in QRS interval was 184 ± 62% in IL group, and 230 ± 56% in control group (NS). Lipid administration reversed the QRS widening previously impaired by bupivacaine. After 10 min of the administration of IL, the mean QRS interval decreased to 132 ± 56% vs. 15 ± 76% relative to the maximum widening induced by bupivacaine, in IL and C group, respectively.

Conclusion: Intralipid reversed the lengthening of QRS interval induced by the injection of bupivacaine. Time to normalization of electrocardiographic parameters can last more than 10 min. While the phenomena of cardiac toxicity persist, resuscitation measures and adequate monitoring should be continued until adequate heart conduction parameters are restored.

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PALABRAS CLAVE
Bupivacaina;
Toxicidad cardíaca;
Intervalo QRS;
Intralipid;
Antídoto

Análisis de la regresión temporal en el ensanchamiento del intervalo QRS inducido por bupivacaina con la administración de Intralipid. Estudio en un modelo experimental porcino

Resumen
Objetivo: La toxicidad cardíaca inducida por la bupivacaina (B) se relaciona con el bloqueo de los canales de sodio, que se traduce por un ensanchamiento del intervalo QRS. Estudios experimentales recientes, sugieren que el Intralipid (IL) es eficaz en revertir la toxicidad cardíaca de la B. Nuestro objetivo fue analizar la evolución temporal del ensanchamiento del QRS inducido por la B con la administración de IL.

Material y método: Doce cerdos fueron anestesiados con tiopental sódico, 5 mg kg⁻¹, y sevoflu-rano a concentración alveolar mínima de 2,6%. Tras la instrumentalización se administró un bolo de B de 4–6 mg kg⁻¹ con el objetivo de inducir un aumento de 150% en la duración del QRS. El grupo IL recibió 1,5 mL kg⁻¹ de IL seguido de 0,25 mL kg min⁻¹; el grupo control (C) recibió salino. Se registraron los parámetros electrocardiográficos tras la infusión de B y a 1, 5,10 y 30 min de la administración de Intralipid/salino.

Resultados: La administración de B (4,33 ± 0.81 mg/kg en el grupo IL y 4,66 ± 1,15 mg/kg en el grupo C) indujo cambios electrocardiográficos similares en ambos grupos; el porcentaje medio de incremento máximo en el QRS fue de 184 ± 62% en el grupo IL, y de 230 ± 56% en el grupo C. El IL revirtió el ensanchamiento del QRS inducido por la B, a los 10 min de su administración el intervalo QRS disminuyó 132 ± 56% vs. 15 ± 76%, en relación al máximo incremento inducido por la B, en el grupo IL y grupo C respectivamente.

Conclusión: El IL revirtió eficazmente el ensanchamiento del intervalo QRS inducido por la B. El tiempo hasta la normalización de los parámetros electrocardiográficos puede prolongarse más de 10 min. Mientras persistan los fenómenos de toxicidad cardíaca, las medidas de resuscitación y monitorización deben continuar hasta que los parámetros de conducción cardíaca se hayan restaurado de forma adecuada.

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Introduction

Bupivacaine, due to its effectiveness, low cost and prolonged action, is still one of the most widely used local anaesthetics (LA). However, it has been associated with cardiac arrest following administration, involving practically simultaneous presentation of seizures and asystole that require prolonged, fruitless, cardiopulmonary resuscitation.

The cardiac toxicity of bupivacaine is due to the combination of acute depression of myocardial contractility and a severe decrease in ventricular conduction, which in turn causes reentrant arrhythmias. Various electrophysiological mechanisms can explain this phenomenon, one of the most relevant being sodium channel block, followed by calcium and potassium channel block to a lesser extent. Electrocardiographically, this sodium channel inhibition manifests as a distinct QRS widening.

In recent years, laboratory studies and individual case reports have suggested that administration of lipids, such as Intralipid (IL), during LA-induced cardiac toxicity can act as an antidote to bupivacaine and potentially reduce...
The intervention, a saline solution (0.9%) was infused at a rate of between 2 and 5 mL·kg⁻¹·h⁻¹. Anaesthesia was maintained with 2.6% sevoflurane, the MAC described for pigs. ¹

An ultrasound-guided (Vivid 55 – GE Healthcare) arterial line was placed in the femoral artery and vein for invasive monitoring and intraoperative determinations.

Continuous 12-lead echocardiography recordings were obtained (ECG Lab 3.0. Tecnomed 2000 S. L. Madrid), together with recording from the standard s lead (PowerLab 16/30, AD Instruments). The continuous recordings were saved to a laptop computer.

Experimental protocol

When the monitoring instruments had been placed and the animal had been stabilized, baseline measurements were taken and a preliminary dose of 4 mg·kg⁻¹ bupivacaine (bupivacaine hydrochloride, Inibsa, Inibsa), was administered over 30 s. The toxic target in our animal model was the induction of cardiac toxicity, which we defined as a 150% increase in the QRS interval. If this was not achieved within 3 min of bupivacaine administration, an additional dose of 1 mg·kg⁻¹ was administered. If the toxic target was not achieved, further doses of 1 mg·kg were administered, up to a total of 6 mg·kg⁻¹.

An initial dose of 1 mg·kg was chosen because this had been shown to give a plasma level of 2000 ng·mL⁻¹ in other bupivacaine-induced cardiac toxicity models. This is usually sufficient to induce severe electrophysiological alterations without causing asystole and the subsequent deterioration of the animal, thus avoiding confounding factors. ², ⁷

When the target toxic effect had been achieved, we proceeded to administer a loading dose of 1.5 mL·kg⁻¹ IL (supplied by the hospital’s pharmacy) injected over 1 min, followed by infusion of 0.25 mL·kg⁻¹ min⁻¹. We used the IL infusion recommended in guidelines published by various anaesthesiology associations for the treatment of local anaesthetic-induced toxicity. In the control group, IL was replaced by saline solution.

We took samples of venous and arterial blood to measure blood gases and bupivacaine levels at the different study time points (GEM® Premier 3000 Blood Gas analyser Model 5700).

Determination of bupivacaine levels

Determination of plasma bupivacaine levels was performed with liquid chromatography-tandem mass spectroscopy (LC–MS/MS), following the method used with other local anaesthetics. For this purpose, a 2 mL sample of venous blood from the femoral vein was centrifuged a 4000rpm for 10 min. All samples were stored frozen at –20 °C until needed for analysis. The analysis was performed with 50 µL of plasma (previously brought up to room temperature) to which mepivacaine was added as an internal standard. We used solid phase extraction (Strata-X columns [3 mL/60 mg]) to eliminate any matrix interference.

Bupivacaine was separated from its internal standard within 1.5 min and quantified using the LC–MS/MS system equipped with an electrospray ionization source in
positive ionization mode. The mass spectrometry method used was MRM (multiple reaction monitoring), in which two phases for both bupivacaine (289.3 > 149.2 and 289.3 > 84.2) and its internal standard (247 > 98 and 247 > 70.1) were monitored.\(^\text{11}\)

**Times and measurements**

Echocardiographic parameters were measured at baseline, following administration of bupivacaine, and then every minute until the toxic target was reached (usually within the first 5 min). After administration of IL, echocardiographic parameters were determined at 1, 5, 10 and 30 min.

**QRS interval duration**: following the standard criteria recommended by the American Heart Association, we considered global intervals in all 12 leads. QRS duration was measured in the lead of earliest onset and up to the lead of latest offset.\(^\text{12}\)

**PR interval**: measured from the beginning of the P wave to the beginning of the Q wave.

**QT interval**: from the beginning of the QRS complex to the end of the T wave.

**Corrected QT interval** (QTc = QT/√RR, Bazett’s formula).

**Statistical analysis**

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results are expressed as median and interquartile range. The general study data and characteristics of study animals were analyzed descriptively.

### Table 1 Haemodynamic parameters at different study time points.

<table>
<thead>
<tr>
<th></th>
<th>Intralipid group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HR, bpm</td>
<td>106 (93–107)</td>
<td>102 (80–108)</td>
<td>0.39</td>
</tr>
<tr>
<td>Baseline SAP (mm Hg)</td>
<td>111 (101–120)</td>
<td>101 (88–111)</td>
<td>0.35</td>
</tr>
<tr>
<td>Baseline DAP (mm Hg)</td>
<td>62 (55–80)</td>
<td>63 (55–69)</td>
<td>0.91</td>
</tr>
<tr>
<td>Bupivacaine HR, bpm</td>
<td>92 (81–99)</td>
<td>83 (69–97)</td>
<td>0.31</td>
</tr>
<tr>
<td>Bupivacaine SAP (mm Hg)</td>
<td>73 (56–96)</td>
<td>76 (62–90)</td>
<td>0.76</td>
</tr>
<tr>
<td>Bupivacaine DAP (mm Hg)</td>
<td>34 (27–61)</td>
<td>40 (33–51)</td>
<td>0.76</td>
</tr>
<tr>
<td>HR 10 min intralipid/saline, bpm</td>
<td>87 (61–103)</td>
<td>98 (68–114)</td>
<td>0.69</td>
</tr>
<tr>
<td>SAP 10 min intralipid/saline (mm Hg)</td>
<td>94 (69–100)</td>
<td>97 (83–107)</td>
<td>0.71</td>
</tr>
<tr>
<td>DAP 10 min intralipid/saline (mm Hg)</td>
<td>47 (36–62)</td>
<td>55 (45–63)</td>
<td>0.54</td>
</tr>
<tr>
<td>HR 30 min intralipid/saline, bpm</td>
<td>97 (54–102)</td>
<td>100 (84–113)</td>
<td>0.54</td>
</tr>
<tr>
<td>SAP 30 min intralipid/saline (mm Hg)</td>
<td>130 (83–140)</td>
<td>113 (101–130)</td>
<td>1</td>
</tr>
<tr>
<td>DAP 30 min intralipid/saline (mm Hg)</td>
<td>82 (45–90)</td>
<td>67 (60–74)</td>
<td>1</td>
</tr>
</tbody>
</table>

DAP, diastolic arterial pressure; HR, heart rate; bpm, beats per minute; SAP, systolic arterial pressure. Data are expressed as median and interquartile range.

### Table 2 Arterial blood gas obtained at different study time points.

<table>
<thead>
<tr>
<th></th>
<th>Intralipid group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline pH</td>
<td>7.52 (7.42–7.53)</td>
<td>7.49 (7.44–7.55)</td>
<td>0.93</td>
</tr>
<tr>
<td>Baseline pO2 (mm Hg)</td>
<td>506 (347–545)</td>
<td>445 (316–542)</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline pCO2 (mm Hg)</td>
<td>34 (31–46)</td>
<td>41 (34–47)</td>
<td>0.48</td>
</tr>
<tr>
<td>Baseline CO2H⁻ (mmol L⁻¹)</td>
<td>28 (21–37)</td>
<td>30 (28–35)</td>
<td>0.60</td>
</tr>
<tr>
<td>Baseline BE (mmol L⁻¹)</td>
<td>6 (3–16)</td>
<td>7 (4–12)</td>
<td>0.74</td>
</tr>
<tr>
<td>Baseline SaO₂ (%)</td>
<td>100</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Bupivacaine pH</td>
<td>7.48 (7.41–7.50)</td>
<td>7.48 (7.45–7.53)</td>
<td>0.61</td>
</tr>
<tr>
<td>Bupivacaine pO2 (mm Hg)</td>
<td>542 (531–545)</td>
<td>488 (474–520)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bupivacaine pCO2 (mm Hg)</td>
<td>42 (40–46)</td>
<td>38 (34–40)</td>
<td>0.1</td>
</tr>
<tr>
<td>Bupivacaine CO2H⁻ (mmol litre⁻¹)</td>
<td>29 (27–37)</td>
<td>28 (27–29)</td>
<td>0.24</td>
</tr>
<tr>
<td>Bupivacaine BE (mmol litre⁻¹)</td>
<td>6 (2.7–10)</td>
<td>5 (4–6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Bupivacaine SaO₂ (%)</td>
<td>100</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Intralipid/saline pH</td>
<td>7.44 (7.38–7.52)</td>
<td>7.46 (7.43–7.55)</td>
<td>0.53</td>
</tr>
<tr>
<td>Intralipid/saline pO2 (mm Hg)</td>
<td>526 (254–577)</td>
<td>483 (422–499)</td>
<td>0.87</td>
</tr>
<tr>
<td>Intralipid/saline pCO2 (mm Hg)</td>
<td>39 (35–44)</td>
<td>40 (32–47)</td>
<td>0.91</td>
</tr>
<tr>
<td>Intralipid/salineCO2H⁻ (mmol L⁻¹)</td>
<td>27 (21–35)</td>
<td>29 (27–30)</td>
<td>0.80</td>
</tr>
<tr>
<td>Intralipid/saline BE (mmol L⁻¹)</td>
<td>3 ± (4–11)</td>
<td>6 (4–8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Intralipid/saline SaO₂ (%)</td>
<td>100</td>
<td>100</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are expressed as median and interquartile range.
QRS values, bupivacaine levels, haemodynamic and blood gas parameters were compared between the IL and control groups using the Mann–Whitney U test for independent samples. QRS values prior to bupivacaine administration, at the moment of maximum toxicity, and following administration of IL were compared using the Wilcoxon test for related samples. Significance levels were not adjusted for multiple comparisons.

Sample size

We estimated that mean QRS widening, on the basis of the bupivacaine dose administered, would be greater the 150% of the baseline value. We considered that a difference of over 50% in the reversal of the QRS value in the Intralipid group vs control would be clinically relevant. We estimated that 6 animals in each group would be sufficient, considering an alpha risk of 0.05 and a beta risk of 0.2.

Results

The mean bupivacaine dose required to produce the QRS interval target was 4.33 ± 0.81 mg/kg in the IL group and 4.66 ± 1.15 mg/kg in the control (C) group, p = 0.59. Haemodynamic and blood gas measurements over the study period are shown in Tables 1 and 2. No significant differences were observed between groups in either of these parameters, except for \(pO_2\) following bupivacaine administration, when this parameter was slightly lower in controls (540 ± 8.6 mm Hg IL group vs 495 ± 28 mm Hg C group).

The evolution of bupivacaine levels over the study period is shown in Fig. 2. Toxic levels in excess of 2000 ng mL\(^{-1}\) were observed in all animals. Plasma levels did not differ between groups.

A significant increase in the QRS interval following administration of bupivacaine was observed. This widened from baseline values of 63 ± 7 ms and 59 ± 11 ms in the IL and C groups, respectively, to 175 ± 29 ms (\(\Delta 177\%\)) in the IL group and 192 ± 29 ms in the C group (\(\Delta 228\%\)); \(p = 0.43\). Fig. 3 shows an example of the effect of bupivacaine on the QRS interval.

Following infusion of IL, QRS widening was reversed in the IL group, but remained the same in the C group (\(p < 0.05\), (Fig. 4). At 10 min after IL administration, the QRS interval decreased to 132 ± 56 ms vs 15 ± 76 ms, relative to the maximum bupivacaine-induced increase observed, \(p = 0.03\). The QRS interval remained significantly widened in the C group at 30 min vs the IL group (Fig. 5). Other electrocardiographic changes are shown in Table 3. The PR interval was prolonged with administration of bupivacaine and partially corrected following IL administration. At 10 min it remained significantly prolonged in the C group (135 ± 19 ms IL group vs 206 ± 24 C group, \(p = 0.002\)). The QTc interval also increased following bupivacaine infusion. However, it did not return to baseline following administration of IL, and at 30 min both groups showed similar values.

![Figure 2 Bupivacaine levels in venous blood. Values expressed as median and interquartile range.](image)

![Figure 3 Example of QRS interval widening following bupivacaine administration. The baseline QRS interval of 50 ms extended to 200 ms following bupivacaine administration.](image)
Arrhythmias were induced in 3 animals from each group. The most common type was complete AV block (1 animal in the IL group and 2 in the C group). Other arrhythmias included nonsustained ventricular tachycardia in 2 animals from the IL group, and 1 episode of sustained ventricular tachycardia in the C group. IL administration reversed the arrhythmia in all animals except for 1, which developed a high-grade AV block with severe hypotension that ended in asystole. This animal received external cardiac massage and 30 μg kg⁻¹, after which its haemodynamic and electrocardiographic parameters were recovered.

**Discussion**

The main finding in this study is that IL was effective in rapidly correcting bupivacaine-induced cardiac conduction toxicity, and in particular in reversing prolongation of the QRS interval.

Bupivacaine-induced depression of cardiac conduction is a well-known phenomenon that manifests on ECG as a widening of the QRS interval.⁵ ¹³ This widening correlates in turn with plasma bupivacaine levels, and is caused by sodium channel block.¹³ Reports from clinical practice have described post-local anaesthesia plasma bupivacaine levels that are high enough to trigger major electrophysiological and haemodynamic alterations. Therefore, a widening of the QRS interval observed in a patient receiving local anaesthetic should prompt clinicians to suspect anaesthetic toxicity, and to take appropriate monitoring and therapeutic measures.
In an earlier study of bupivacaine toxicity in a porcine model similar to ours, the authors compared the effects of early administration of two lipid preparations vs saline solution on cardiac conduction. This study showed that early (30s post-bupivacaine) infusion of lipids can reverse bupivacaine-induced electrophysiological and electrocardiographic alterations. In contrast to this study, in our bupivacaine toxicity model we specifically sought to reproduce a situation of severe cardiac toxicity with a mean widening of the QRS interval of over 150% over baseline. Once this target toxicity had been achieved, we administered IL. This cardiac conduction delay impairs the electrical and mechanical activation of the left ventricle, a depolarisation that could in turn trigger reentrant arrhythmia. In our study, IL successfully restored electrical conduction after the toxic effects of bupivacaine administration had been confirmed, thus adding further evidence to support the administration of lipid solutions in the event of accidental bupivacaine intoxication. However, it is important to note that the effect of bupivacaine on the QRS interval persists 10 min after IL administration. This finding, together with the persistence of other electrocardiographic alterations up to 30 min after IL infusion, suggests the need for continued clinical monitoring due to the continued vulnerability of the heart.

Our findings are consistent with those of earlier studies showing that IL reverses bupivacaine-induced cardiac arrest and myocardial depression. In dogs given higher toxic doses of bupivacaine that those used in our study, IL infusion associated with other cardiopulmonary resuscitation measures increased the survival rate in the treatment group vs controls not receiving lipids. Similarly, pre-treatment with lipids in rats receiving bupivacaine increased the dose of bupivacaine required to cause death in 50% of animals by 48%. Generally speaking, most authors have found that lipid administration improve both survival and the effectiveness of resuscitation measures in vivo models, and facilitates the restoration of cardiac parameters in isolated heart models.

Several reports concerning patients presenting severe LA intoxication have shown that lipid administration facilitated patient recovery, often when other resuscitation measures had failed. The protective mechanism of lipids against toxicity from long acting LA suggests they are lipophilic, and shows the excellent capacity of lipid emulsions to bind with LAs. The most widely accepted theory in this regard is Weinberg’s lipid sink phenomenon, which suggests that a tissue-blood concentration gradient is established that drives the LA drug from the heart and other tissues into the newly formed ‘lipid sink. Other mechanisms suggested involve an increase in intracellular fatty acid content that overcomes the reduced ATP production caused by LA-induced blockade of fatty acid transport and oxidation. Despite these theories, further research is needed to definitively explain the mechanism responsible for the anti-LA toxicity action of lipid emulsions.

**Clinical considerations**

Extraordinary progress has been made in recent years in local anaesthesia techniques in response to a growing demand from both patients and surgeons. Despite their proven efficacy, however, the risk of systemic toxicity has been a recurring problem since LAs were first introduced into clinical practice. The findings of our study support those of earlier authors who showed that IL reverses the cardiac conduction alterations induced by bupivacaine toxicity. We also found that cardiac toxicity persists for at least 10 min...
after IL infusion, suggesting that patients should remain under observation until they are stabilized and out of danger. It is essential to take precaution to avoid adverse events when administering local anaesthesia. However, should cardiac toxicity occur, administration of a lipid emulsion should be considered to reverse the toxic effects of bupivacaine on cardiac electrical conduction.

Limitations

In our study, we did not evaluate the mechanism of action of Intralipid, and therefore we cannot specifically confirm the action of this emulsion. However, the existence of a control group in which cardiac toxicity was not reversed would corroborate the effectiveness of the antidote. Likewise, we cannot be sure whether cardiac recovery can be extrapolated to a model with a higher dose of bupivacaine and higher level of cardiac toxicity. However, the electrocardiographic parameters obtained showed that the levels obtained in this study were sufficiently toxic, and this in our opinion justifies our conclusions.

Conclusions

This study has shown that administration of Intralipid effectively reverses the cardiac toxicity induced by non-lethal doses of bupivacaine. These findings justify the use of Intralipid in situations of bupivacaine toxicity, and supports the recommendations made in toxicity management guidelines. This does not rule out, however, the need for concomitant cardiopulmonary resuscitation measures in cases of severe toxicity.

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Conflict of interests

The authors declare no conflict of interest relating to the content of this study.

References

Temporal regression analysis of the QRS widening induced by bupivacaine

