FUNCTIONAL AND METABOLIC EFFECTS OF BUPIVACAINE AND LIGNOCAINE IN THE RAT HEART-LUNG PREPARATION

S. KASHIMOTO, M. KUME AND T. KUMAZAWA

SUMMARY

We have examined the effects of bupivacaine and lignocaine on myocardial metabolism in the rat isolated heart-lung preparation. Bupivacaine 1, 5 or 25 μg ml⁻¹ or lignocaine 4, 20 or 100 μg ml⁻¹ was administered 5 min after the start of perfusion. Both bupivacaine 25 μg ml⁻¹ and lignocaine 100 μg ml⁻¹ reduced heart rate significantly. Bupivacaine 25 μg ml⁻¹ was associated with a higher incidence of arrhythmias than the other groups. Three hearts in the bupivacaine 25 μg ml⁻¹ group (n = 8) and two hearts in the lignocaine 100 μg ml⁻¹ group (n = 8) failed (zero cardiac output) at the end of the experiment. Although there were no significant differences in myocardial lactate and glycogen concentrations between groups, ATP content in the bupivacaine 25 μg ml⁻¹ and lignocaine 100 μg ml⁻¹ groups was significantly less than that in the control group. The results suggest that myocardial depression and subsequent metabolic deterioration occurred with both the high doses of local anaesthetics; these findings do not account for the apparent increased cardiotoxicity of bupivacaine.

KEY WORDS


In 1979, Albright suggested that bupivacaine and etidocaine are more selectively cardiodepressant than agents such as lignocaine [1]. This report led to considerable animal experimentation in an effort to clarify the mechanisms by which bupivacaine may cause cardiodepression, ventricular arrhythmias, cardiac arrest and death. Some investigators reported that the degree of cardiovascular depression is related to anaesthetic potency [2–6], while others have suggested that bupivacaine has a greater cardiovascular toxicity and a lesser margin of safety [7–11].

Many studies have assessed the cardiovascular effects of local anaesthetics. However, the direct effects of local anaesthetics on the heart are obscured by sympathetic activation caused by CNS effects [12]. Therefore, some studies have been performed in intact animals by giving the drugs into a coronary artery in order to separate CNS and cardiac effects of local anaesthetics [3, 6].

This study was designed to evaluate the functional and metabolic changes induced by bupivacaine and lignocaine in the rat isolated heart-lung preparation. This technique obviates confounding neurohumoral effects of in vivo studies.

MATERIALS AND METHODS

The experiment was performed in accordance with Guidelines for Animal Experiments, Yamanashi Medical College. The techniques used were identical to those used earlier [13]. Briefly, 56 male Wistar–Kyoto rats (300–320 g) were anaesthetized with pentobarbitone 50 mg kg⁻¹ i.p. Tracheotomy was performed, and intermittent positive pressure ventilation was instituted with air. The chest was opened and flooded with ice-cold saline and the heart arrested. Cannulae were inserted into the aorta and the superior (for measurement of central venous pressure) and inferior venae cavae.

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The heart-lung preparation was perfused with a solution containing red blood cells collected from another rat and Krebs Ringer bicarbonate buffer, with PCV 25% and pH 7.4. The concentrations (mmol litre⁻¹) of the buffer constituents were: NaCl 127, KCl 5.1, CaCl₂ 2.2, KH₂PO₄ 1.3, MgSO₄ 2.6, NaHCO₃ 15 and heparin. The perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir kept at 37°C and returned to the inferior vena cava. In this model, no other organs except heart and lung were perfused. Cardiac output was determined by the inflow, provided the heart did not fail, and systolic arterial pressure was regulated by pneumatic resistance.

Heart rate was recorded with a bioelectric amplifier (Nihon Kohden AB-621G) and cardiac output was measured with an electromagnetic flow meter (MFV-1200). Arterial and right atrial pressures were measured with transducers (TP101T and LPU-0.1A) and carrier amplifiers (AP-621G).

All hearts were perfused initially with a cardiac output of 30 ml min⁻¹ and systolic arterial pressure 80 mm Hg. Five minutes after the start of perfusion, bupivacaine 1 µg ml⁻¹, 5 µg ml⁻¹ or 25 µg ml⁻¹, or lignocaine 4 µg ml⁻¹, 20 µg ml⁻¹ or 100 µg ml⁻¹ was added to the reservoir except in the control group. Eight animals were studied in each of the seven groups which were denoted according to the dose of local anaesthetics: B1, B5, B25, L4, L20, L100 and C. During perfusion, atrioventricular (A-V) block was defined as asynchrony of atrial and ventricular electrical activity.

Thirty minutes after the start of the study, hearts were freeze-clamped and freeze-dried for 6 days. An aliquot was extracted with perchloric acid and centrifuged at 3000 g. Concentrations of ATP and lactate were measured spectrophotometrically by standard techniques [14]. Another piece of freeze-dried sample was placed in 30% potassium hydroxide and digested at 100°C. Tissue glycogen was extracted, hydrolysed and assayed as glucose equivalents [15]. The values were expressed as µmol/g dry weight.

Statistical analysis used one-way analysis of variance followed by the Dunnett test. The incidence of A-V block, ventricular rhythm or stand still was analysed by chi-square test. A probability of \(P < 0.05\) was regarded as statistically significant. The data are given as means (SD).

**RESULTS**

One heart in each of the B1, B5 and L20 groups failed immediately after the administration of drugs. However, they recovered at the end of the experiment. Three hearts in the B25 group and two in the L100 group failed to recover (zero cardiac output) at the end of the experiment (figs 1,2) and are excluded from analysis of heart rate changes.

Because there was considerable variability between animals in control values of heart rate, values after administration of drug are presented as the percentage mean changes from baseline values. Heart rate decreased significantly in the B25 and L100 groups after administration of drug (table I).

The incidence of A-V block, ventricular
Table I. Percentage changes in heart rate from baseline values. B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml⁻¹, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml⁻¹, respectively. n = 8 each group except as specified. *P < 0.05 vs control

<table>
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<td>Control</td>
<td>106 (7)</td>
<td>108 (6)</td>
<td>102 (9)</td>
<td>100 (11)</td>
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<td>96 (8)</td>
<td>88 (9)</td>
<td>85 (7)</td>
<td>82 (10)</td>
<td>74 (18)*</td>
<td>75 (18)</td>
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<tr>
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<td>105 (8)</td>
<td>82 (28)*</td>
<td>81 (24)</td>
<td>80 (16)</td>
<td>82 (11)</td>
<td>81 (12)</td>
</tr>
<tr>
<td>B25</td>
<td>103 (12)</td>
<td>37 (26)*</td>
<td>42 (29)*</td>
<td>45 (26)*</td>
<td>45 (18)*</td>
<td>50 (21)*</td>
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<tr>
<td>L4</td>
<td>104 (6)</td>
<td>99 (6)</td>
<td>97 (9)</td>
<td>95 (9)</td>
<td>93 (9)</td>
<td>94 (14)</td>
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<tr>
<td>L20</td>
<td>114 (14)</td>
<td>102 (24)</td>
<td>88 (34)</td>
<td>94 (13)</td>
<td>95 (11)</td>
<td>96 (12)</td>
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<tr>
<td>L100</td>
<td>103 (15)</td>
<td>29 (14)*</td>
<td>40 (22)*</td>
<td>50 (27)*</td>
<td>53 (24)*</td>
<td>61 (21)*</td>
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Table II. Incidence of A-V block, ventricular rhythm or cardiac arrest. B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml⁻¹, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml⁻¹. n = 8 each group. *P < 0.05 vs other groups

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Fig. 2. Changes in cardiac output (CO) after administration of lignocaine (n = 8 each group).

Fig. 3. Myocardial concentrations of lactate (n = 8 each group). C = Control; B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml⁻¹, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml⁻¹, respectively.
However, there were almost no differences in cardiac output, heart rate changes or myocardial metabolism between equianalgesic doses of bupivacaine and lignocaine. Other investigators have reported that cardiovascular toxicity of bupivacaine is either comparable to its anaesthetic potency [2-6,12] or greater than that of lignocaine [7-11].

In the isolated rat heart, Komai and Rusy demonstrated that the ratio between bupivacaine and lignocaine for slowing ventricular rate to 50% of control was 14:1 [7]. Tanz and colleagues [8] concluded that 3 μg ml⁻¹ of unbound bupivacaine was more cardiotoxic than 30 μg ml⁻¹ of unbound lignocaine in the isolated guineapig heart. Lynch [11] found a 10:1 ratio (lignocaine:bupivacaine) for equal contractile depression in isolated guineapig papillary muscle. In the isolated canine heart, the depression of contraction ratio was 8.1:1 (L:B) [16]. In an in vivo study, Rosen and others [10] demonstrated that bupivacaine was more cardiotoxic than lignocaine, and that in sheep this toxicity was enhanced by hypercarbia, acidosis and hypoxia. Recently, Nancarrow and colleagues [17] also have reported greater cardiotoxicity of bupivacaine compared with lignocaine in the sheep.

In contrast, Nath and colleagues [3] studied anaesthetized pigs and found dose-dependent depression of the left ventricle in the same ratio as anaesthetic potency (B:L = 4:1), although comparable prolongations of the QRS interval with bupivacaine and lignocaine were obtained at a dose ratio of 1:16. Recent studies also have reported that the degree of cardiotoxicity of local anaesthetics was related to anaesthetic potency [4-6].

This difference may result from several factors. First, bupivacaine is more likely than lignocaine to cause sodium channel block [9], A-V conduction block [7,18] and ventricular arrhythmias [12,16, 19-23]. These results are consistent with ours. Second, it may be attributed to species differences. For example, Kasten and Martin [24] demonstrated that sheep are more sensitive to bupivacaine than are dogs. In addition, bupivacaine is less toxic than lignocaine in mice when given i.p. [25]

Differences may result from the use of non-blood perfusion medium in the isolated preparations. However, Cronau and co-workers [26] reported that, in the working rat heart model, the acute depressant effects of bupivacaine and ligno-
caine on cardiac function were exerted in a potency ratio of approximately 4.59. This is similar to anaesthetic potency. Finally, it has been suggested that the CNS is the primary target organ for the toxic effects of local anaesthetics [27], and that the CNS plays a role in mediation of the cardiovascular system toxicity of local anaesthetics [28]. Heavner [22] provided evidence that the CNS effects of bupivacaine, but not lignocaine, induced ventricular arrhythmias in cats (independent of direct cardiac effects) when injected into the cerebral ventricle. However, Kotelko and others [20] observed that equivalent doses of lignocaine or bupivacaine produced similar CNS toxicity when injected rapidly i.v. in conscious sheep.

Although Eledjam and colleagues [29] suggested that inhibition of energy metabolism is a major mechanism of cardiac depression produced by bupivacaine, local anaesthetics do not exert depressant effects by influencing tissue high energy phosphate content [26]. In our study, there were no significant differences in myocardial lactate and glycogen concentrations between groups. However, ATP contents in the highest dose groups were significantly less than that in the control group. This may be a reflection of the fact that three and two hearts in the highest dose groups failed to recover at the end of the experiment, as ATP concentrations in the non-failed hearts of the B25 and L100 groups were 17.1 (2.2) and 17.4 (1.3) µmol g⁻¹, respectively. These data were not significantly different from those in the control group. From these results, we speculate that high doses of local anaesthetics may depress cardiac contractility and thereby reduce the myocardial content of ATP.

REFERENCES
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