Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine

G. Lyons, M. Columb, R. C. Wilson and R. V. Johnson

Summary

We have compared the minimum local analgesic concentrations (MLAC) of levobupivacaine relative to racemic bupivacaine in a prospective, randomized, double-blind, sequential allocation study. Women in labour were given a 20-ml bolus of epidural levobupivacaine or bupivacaine diluted to a concentration determined by up–down sequential allocation. The initial concentration was 0.07% w/v for both drugs. Efficacy was defined using a visual analogue pain score (VAPS) at 10 mm or less within 30 min. The MLAC of levobupivacaine was 0.083% w/v (95% CI 0.065–0.101) and the MLAC of bupivacaine 0.081% w/v (95% CI 0.055–0.108). In molar terms, the MLAC of levobupivacaine was 2.87 mmol litre⁻¹ (95% CI 2.25–3.49) and the MLAC of bupivacaine 2.49 mmol litre⁻¹ (95% CI 1.69–3.32). With regard to the commercial preparations, the potency ratio levobupivacaine:bupivacaine was 0.98 (95% CI 0.67–1.41), and this is unlikely to be of clinical relevance. In molar terms, the ratio was 0.87 (95% CI 0.60–1.25). With regard to toxicity, the evidence should be evaluated in the light of a possible 13% potency difference in molar concentration in favour of racemic bupivacaine. (Br. J. Anaesth. 1998; 81: 899–901).

Keywords: analgesia, obstetric; analgesic techniques, epidural; anaesthetics local, bupivacaine; pharmacokinetics, stereoisomers

In 1979, Albright drew attention to a number of maternal deaths after accidental i.v. injection of bupivacaine intended for the epidural space.¹ In the UK, the problem manifested itself in deaths during i.v. regional anaesthesia (IVRA) with bupivacaine.² Subsequent recommendations led to the withdrawal of bupivacaine for IVRA, and the 0.75% w/v concentration of this anaesthetic in the first stage of labour. We excluded those in whom cervical dilatation exceeded 5 cm and those who had received opioid or sedative drugs. The use of a transcutaneous electrical nerve stimulator or Entonox before epidural request was not regarded as a need to exclude.

I.v. saline 0.9% w/v was infused via a forearm cannula. The epidural space was found using an 18-gauge Tuohy needle at either L2–3 or L3–4 in the sitting position. Loss of resistance to saline was used to identify the epidural space, limiting injection to 2 ml in order to minimize dilution of local anaesthetic. For the purpose of the study, the test dose was omitted.

The first administration of levobupivacaine or bupivacaine was in a freshly prepared syringe containing 20 ml of test solution given over 5 min. Local anaesthetic was diluted with 0.9% w/v saline to achieve the desired concentration at room temperature.

Women were allocated randomly to one of two Concurrent groups to receive levobupivacaine (n = 30) or bupivacaine (n = 30). The concentration of local anaesthetic in the first syringe of each group was 0.07% w/v. This corresponded to a previously determined MLAC for bupivacaine.³ Thereafter, the concentration of the test solution in each individual syringe was determined by the response of the previous patient in the same group to the higher or lower concentration in her test syringe, according to up–down sequential allocation. Maternal heart rate, arterial pressure, uterine contractions and fetal heart rate were monitored.

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Efficacy of the first dose was assessed using a 100-mm visual analogue pain score (VAPS) where 0 represented “no pain” and 100, “worst pain ever”, at 5-min intervals up to 30 min after injection of the test solution (first bolus). Three outcomes were possible: (1) effective, this required that the VAPS decreased to 10 mm or less at the height of contraction, within 30 min, and indicated the end of the study and directed a decrement of 0.01% w/v local anaesthetic for the next woman; (2) ineffective, this followed failure of the VAPS to reach 10 mm within 30 min of the test solution. Rescue analgesia consisting of 0.25% bupivacaine 15 ml was given. After this, a reduction in VAPS to 10 mm or less indicated the end of the study and directed a 0.01% increment for the next woman; (3) repeat, failure to achieve a VAPS of 10 mm after rescue directed that the same concentration be repeated for the next woman.

For all women, age, weight, height, gestation, parity, cervical dilatation, use of oxytocin infusion and presence of pruritus were recorded.

A modified Bromage score (0 = no impairment, 1 = inability to raise leg, 2 = inability to flex knee and 3 = complete paralysis) was performed on all women, either at 30 min after an effective outcome or after rescue when an ineffective outcome had been reached. If the score for both legs was zero, women were mobilized and ability to stand unaided, walk unaided and perform a knee bend was recorded.

The source of racemic bupivacaine was the commercial preparation (Marcain, Astra) expressed as anhydrous bupivacaine hydrochloride containing 2.64 mg ml⁻¹ of bupivacaine hydrochloride monohydrate corresponding to 2.12 mg ml⁻¹ (7.7 mmol litre⁻¹) of free base. The source of levobupivacaine (Chirocaine, Chiroscience) was expressed as anhydrous pure base containing 2.50 mg ml⁻¹ (8.6 mmol litre⁻¹) of free base.

Patient and obstetric data were collected and are presented as mean (SD) and median (interquartile range), as appropriate. Median effective concentrations were estimated from the up–down sequences using the formula of Dixon and Massey which predates this directive, and an ampoule of the same concentration contains bupivacaine hydrochloride 2.5 mg ml⁻¹ of free base. The potency difference widens to 13%. Although the directive is only applicable to countries in the EEC, this required that formulations of hydrates and salts must be expressed as milligrams of active moiety. Our ampoules of levobupivacaine 0.25% w/v contained 2.5 mg ml⁻¹ of free base. Registration of racemic bupivacaine predates this directive, and an ampoule of the same concentration contains bupivacaine hydrochloride 2.5 mg ml⁻¹. Because of this, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of the same concentration of bupivacaine, and when this is taken into account, the potency difference widens to 13%. Although the Directive is only applicable to countries in the EEC, this required that formulations of hydrates and salts must be expressed as milligrams of active moiety. Our ampoules of levobupivacaine 0.25% w/v contained 2.5 mg ml⁻¹ of free base. Registration of racemic bupivacaine predates this directive, and an ampoule of the same concentration contains bupivacaine hydrochloride 2.5 mg ml⁻¹. Because of this, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of the same concentration of bupivacaine, and when this is taken into account, the potency difference widens to 13%. Although the Directive is only applicable to countries in the EEC, this required that formulations of hydrates and salts must be expressed as milligrams of active moiety. Our ampoules of levobupivacaine 0.25% w/v contained 2.5 mg ml⁻¹ of free base. Registration of racemic bupivacaine predates this directive, and an ampoule of the same concentration contains bupivacaine hydrochloride 2.5 mg ml⁻¹. Because of this, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of the same concentration of bupivacaine, and when this is taken into account, the potency difference widens to 13%. Although the Directive is only applicable to countries in the

### Results

We enrolled 73 women in the study. Six women in each group were withdrawn because of study violations, and one patient in the bupivacaine group because of failure of rescue. Thus 60 women were evaluated. The groups were similar in patient and obstetric characteristics (table 1).

Using the formula of Dixon and Massey, the MLAC of levobupivacaine was 0.083% w/v (95% CI 0.065–0.101) and the MLAC of racemic bupivacaine 0.081% w/v (95% CI 0.055–0.108) The relative potency of levobupivacaine to racemic bupivacaine was 0.98 (95% CI 0.67–1.41) (fig 1, 2).

In terms of molar concentrations, the MLAC of levobupivacaine was 2.87 (95% CI 2.25–3.49) mmol litre⁻¹ and the MLAC of racemic bupivacaine 2.49 (95% CI 1.69–3.32) mmol litre⁻¹. The molar potency ratio was 0.87 (95% CI 0.60–1.25). The derived dose–response point estimates are illustrated in figure 3.

Fifteen women in the levobupivacaine group had motor scores of 0 compared with 12 after racemic bupivacaine (ns). All women with 0 scores were able to stand and walk unaided, and perform a knee bend.

### Discussion

We have shown a 2% difference in potency between the two commercial preparations in favour of racemic bupivacaine. This is unlikely to be of clinical relevance. Levobupivacaine is bound by Directive 91/507 of the European Economic Community, part 2, section A, clause 3.3, which stipulates that formulations of hydrates and salts must be expressed as milligrams of active moiety. Our ampoules of levobupivacaine 0.25% w/v contained 2.5 mg ml⁻¹ of free base. Registration of racemic bupivacaine predates this directive, and an ampoule of the same concentration contains bupivacaine hydrochloride 2.5 mg ml⁻¹. Because of this, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of the same concentration of bupivacaine, and when this is taken into account, the potency difference widens to 13%. Although the Directive is only applicable to countries in the

### Table 1 Patient and obstetric data (mean (SD), median [interquartile range] or number). VAPS = Visual analogue pain scores

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine (n = 30)</th>
<th>Levobupivacaine (n = 30)</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>26.9 (18–37)</td>
<td>26.8 (18–35)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (6.52)</td>
<td>163 (6.67)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.5 (14.0)</td>
<td>73.4 (12.5)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>39 (39–40)</td>
<td>40 (40–41)</td>
</tr>
<tr>
<td>Cervical dilatation (cm)</td>
<td>3 [3–4]</td>
<td>3 [2–3]</td>
</tr>
<tr>
<td>Parity</td>
<td>0 [0–1]</td>
<td>0 [0–1]</td>
</tr>
<tr>
<td>Nulliparous/multiparous</td>
<td>16/14</td>
<td>21/9</td>
</tr>
<tr>
<td>Oxytocin infused</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Initial VAPS (mm)</td>
<td>66 [45–84]</td>
<td>72 [46–89]</td>
</tr>
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![Figure 1](image-url)
European Community, it is likely that the European formulation will become universal.

Another potency comparison was that of Aps and Reynolds who conducted an intradermal study with levobupivacaine and dexbupivacaine in human volunteers. They found that levobupivacaine was more potent. This can be explained by differences in vasoactivity. There is a tendency for S(-) enantiomers to produce more vasoconstriction at low concentrations, and this could explain the finding.10 The addition of vasoconstrictors to epidural bupivacaine has little clinical effect11 and gives reason to believe that performance in the epidural space is unlikely to be influenced by vasoconstriction.

Toxicity studies performed in animals have shown that both the convulsive and lethal doses of the S(-) enantiomer are greater than those for racemic bupivacaine.12 13 When given i.v. to 12 human volunteers at a rate of 10 mg min⁻¹, plasma concentrations of levobupivacaine and racemic bupivacaine at the end of the infusion were 2.38 μg ml⁻¹ and 1.87 μg ml⁻¹, respectively. Mean total tolerated doses were 54 mg of levobupivacaine and 45.6 mg of racemic bupivacaine. Thoracic bioimpedance recorded decreases in stroke index, acceleration index and ejection fraction that were greater with racemic bupivacaine compared with levobupivacaine, and this difference was statistically significant.14 In this study, the dosing regimen was adjusted to accommodate differences in weight/volume expression between the local anaesthetics.

In summary, we have shown that with regard to commercial preparations, levobupivacaine was 2% less potent than racemic bupivacaine, but this is unlikely to be clinically important. Because of differences in the weight/volume expression of the two local anaesthetics, there is a possible 13% difference in the potencies of the molar concentrations, and this must be borne in mind when toxicity studies are evaluated.

Acknowledgement
This study was commissioned by Chiroscience who supplied Chirocaine (0.25% w/v levobupivacaine as the hydrochloride salt).

References