Comparison of ropivacaine and bupivacaine in extradural analgesia for the relief of pain in labour

A. F. McCrae, H. Jozwiak and J. H. McClure

Summary

Forty women having requested extradural analgesia for labour were allocated randomly to receive 0.5% ropivacaine or bupivacaine 10 ml as the main dose. When a top-up was requested, 0.25% ropivacaine or bupivacaine 10 ml was given (the same drug as the main dose). The study ended when a second top-up was requested or delivery of the baby occurred. Pain from two contractions was assessed before extradural block by visual analogue scoring and thereafter with every contraction. Sensory block and motor block were assessed at intervals. The only significant difference between the groups was a shorter onset of pain relief after the main dose of bupivacaine; there were no other significant differences in duration, onset of pain relief after top-up, quality of analgesia, spread of sensory block and motor block between the groups. Cardiovascular changes and neonatal outcome were similar in the two groups (Br. J. Anaesth. 1995; 74: 261-265)

Key words

The ability to synthesize pure forms of isomers and stereoselective drug assays have allowed development of single isomer drugs. Ropivacaine (s-(−)-1-propyl-2'-6'-pipocexoloylislde hydrochloride monohydrate), a new amide local anaesthetic, is a single isomer drug. Ropivacaine is prepared as the s(−)- or laevo form, rather than as a racemic mixture (e.g. bupivacaine and mepivacaine). Ropivacaine is chemically similar to bupivacaine, the butyl group being replaced by a propyl group.

Bupivacaine is the most commonly used local anaesthetic in extradural analgesia for labour. The predominant sensory block which occurs with bupivacaine makes it suitable for use as an analgesic in labour, but motor block does occur and there is also potential for cardiotoxicity and central nervous system (CNS) toxicity [1, 2].

Ropivacaine has been shown to have an increased therapeutic index (ratio between local anaesthetic and toxic effects) in laboratory, animal and human volunteer studies. In a preparation of isolated, perfused rabbit heart, ropivacaine was less cardiodepressant and less arrhythmogenic than bupivacaine [3]. In dogs receiving i.v. infusions of ropivacaine or bupivacaine, the convulsive dose was similar for the two drugs. Infusion of twice the convulsive dose of bupivacaine produced arrhythmias in five of six dogs, of which five died, whereas infusion of twice the convulsive dose of ropivacaine produced arrhythmias in two of six dogs and only one died [4]. In a subsequent study, an attempt was made to resuscitate the dogs. In the bupivacaine group two of six were resistant to treatment but all dogs given ropivacaine were resuscitated successfully [5]. In human volunteer studies, an i.v. infusion of ropivacaine or bupivacaine was continued until the subject was aware of signs of toxicity or until a limit of 150 mg had been given. Ropivacaine was less toxic to the CNS as 25% more drug was tolerated. Both drugs depressed cardiac conduction and contractility, but this occurred at lower doses and at lower plasma concentrations with bupivacaine than ropivacaine [6]. Therefore, ropivacaine is thought to have a greater margin of safety if a large dose is injected i.v. by accident.

I.v. infusion of ropivacaine to determine the dose and plasma concentration at which each of the toxic manifestations occurred was accompanied by no significant differences between pregnant and non-pregnant sheep [7]. This was in contrast with bupivacaine where toxic manifestations occurred at lower doses and at lower plasma concentrations in pregnant compared with non-pregnant ewes [8]. Thus ropivacaine may be safer than bupivacaine in pregnant patients.

Ropivacaine has been shown to have similar pharmacokinetic and pharmacodynamic properties as bupivacaine. After extradural administration in dogs, there were no significant differences between bupivacaine and ropivacaine in C \text{max} \ \ T_1 \ \ \text{and total body clearance} [9].

Most studies have found no significant difference in onset, duration or maximum height of sensory block after extradural anaesthesia with ropivacaine or bupivacaine, and the majority of studies found that ropivacaine produced a less intense motor block than bupivacaine [10].

The aim of this study was to compare the sensory and motor blocking effects of ropivacaine with those

of bupivacaine when used for extradural analgesia in labour.

Patients and methods
This double-blind study was approved by the Anaesthetic Subcommitte of the Lothian Health Board Ethics Review Committee. Written informed consent was obtained before the onset of painful labour from 43 women who had chosen extradural analgesia, and who had not received parenteral analgesia in the preceding 12 h. All patients were at term after an uncomplicated pregnancy, 18-36 years of age, weighed less than 100 kg, were taller than 150 cm and were ASA grade I.

Patients were allocated randomly to receive either 0.5 % ropivacaine or bupivacaine 10 ml to establish the block followed by a second 10-ml dose of the same drug at a concentration of 0.25 %, when a top-up was required. The study ended when a second top-up was requested or at delivery, whichever occurred first. If labour continued beyond the study period, subsequent top-ups in both groups were with bupivacaine as indicated clinically and according to current unit practice. An i.v. infusion of Hartmann's solution was commenced, but volume pre-loading was not performed routinely. The extradural space was located at the L2–3 vertebral interspace with the patient in the sitting or lateral position using a midline approach with a 16-gauge Tuohy needle and loss of resistance to less than 4 ml of saline. An end-holed catheter was directed 3 cm cephalad in the extradural space and then taped to the skin. The patient was turned to the right lateral position and a test dose of 0.5 % ropivacaine or bupivacaine 4 ml from identical ampoules coded by number was injected at a rate of 1 ml/2 s. Five minutes later the patient was turned to the left lateral position and another 6 ml of local anaesthetic injected. When a top-up was requested, 0.25 % ropivacaine or bupivacaine 10 ml was given over 1 min with the patient in the supine wedged position. (All extradurals were sited by one of four consultant obstetric anaesthetists.)

Pain of contractions was assessed using a visual analogue scale (VAS) of 100 mm and also a verbal rating score of “painful”, “aware but not painful” or “unaware”. All patients were asked to complete a VAS and verbal rating score for two contractions before the extradural and then with every contraction during the study period. Maternal heart rate and arterial pressure were recorded before the study began, at 5, 10, 15, 20 and 30 min after the main dose and top-up, and otherwise every 30 min during the study. Fetal heart rate was monitored continuously on a cardiotocograph and recorded at the same intervals as maternal cardiovascular variables. Maternal hypotension was defined as systolic arterial pressure less than 90 mmHg.

Sensory analgesia to pinprick was assessed using a 27-gauge, short-bevelled dental needle at 15, 30, 45 and 60 min after the main dose and top-up, and otherwise at 30-min intervals during the study. Motor block was assessed by a modified Bromage scale. An overall evaluation of the quality of analgesia was made by the investigator 30 min after the main dose and 30 min after the top-up, and a global evaluation at the end of the study was made. All assessments were carried out by one investigator (A.F.M.).

The mode of delivery was recorded and also neonatal Apgar scores at 1 and 5 min. Any adverse events were recorded both during the study and the entire hospital stay. Patients were contacted at home by telephone or letter 1–2 weeks after delivery for follow-up.

Onset of pain relief was determined from the first report of being aware of a painless contraction or of being unaware of the contraction, which was identified on the cardiotocograph. Duration was assessed by the return of two successive painful contractions. These timings were confirmed by reference to concurrent VAS scores.

Data management and statistical analysis were performed at Astra Pain Control AB, Sodertalje. The database used was Oracle and the SAS system version 6.07 was used in statistical analysis of clinical efficacy and adverse events. Onset duration and visual analogue scores were compared using the Wilcoxon rank sum statistic. All tests were two-tailed. \( P = 0.05 \) was taken as significant.

Results
We studied 43 patients; 22 received ropivacaine and 21 bupivacaine. Three were excluded from efficacy analysis because of technical problems (two patients had unilateral blocks and one had a paravertebral block); thus there were 20 patients in each group for efficacy evaluation. The groups were well matched for age, height, weight and ratio of primiparae to multiparae (table 1). All patients received the main dose (0.5 % ropivacaine or bupivacaine 10 ml), and a top-up dose of 0.25 % ropivacaine 10 ml was given to 20 patients and 0.25 % bupivacaine 10 ml to 18 patients. (Two patients in the bupivacaine group delivered before requesting a top-up.)

Onset
The median onset time for pain relief after the main dose was 18 (range 7–27) min in the ropivacaine group and 12 (3–24) min in the bupivacaine group (\( P < 0.05 \)). The onset of pain relief following the top-up dose was shorter in both groups and was 9.5 (3–31) min in the ropivacaine group and 8 (2–23) min in the bupivacaine group (ns) (table 2).

Duration
The median duration of pain relief after the main dose was 52 (0–129) min in the ropivacaine group and 64.5 (0–147) min in the bupivacaine group. After the top-up dose, the median durations were 89 (0–147) min and 69 (0–142) min, respectively (ns) (table 2).

Spread of sensory block
The median maximum spread of analgesia was T9–S2 in the ropivacaine group and T9–S1 in the bupivacaine group. After the top-up the median
Table 1  Patient characteristics (mean (SD or range) or number). No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Ropivacaine (n = 20)</th>
<th>Bupivacaine (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>25.2 (18-34)</td>
<td>26.7 (20-35)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.5 (5.9)</td>
<td>162.6 (6.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.2 (9.8)</td>
<td>80.6 (10.3)</td>
</tr>
<tr>
<td>Primiparae: multiparae</td>
<td>16:4</td>
<td>15:5</td>
</tr>
</tbody>
</table>

maximum spread was T8–S5 in both groups (table 2).

QUALITY OF ANALGESIA

Global evaluation of the quality of analgesia was good in most of the patients, as judged by the investigator (table 3). The mean VAS score before the extradural was 84 (28–100) mm in the ropivacaine group and 69.5 (26–99) mm in the bupivacaine group (ns). Before the top-up dose mean VAS was 42 (16–100) mm in the ropivacaine group 31.5 (8–96) mm in the bupivacaine group (ns). All VAS scores observed for each patient during the period was selected and from this the mean VAS for each patient during this period was calculated to produce the mean VAS at 30–60 min after the main dose and top-up dose. This showed very wide variation, although most of the patients had a mean score of less than 20 mm (table 3). There were no differences between the groups in this respect. To show the development of the block over time, individual VAS data were plotted against the midpoint of the intervals 0–10, 10–20, 20–30, 30–40 min, etc. Thereafter, the median VAS was calculated for each midpoint in time and the median values were connected by a smooth curve (fig. 1).

MOTOR BLOCK

In the ropivacaine group, motor block was grade 0 in seven, grade 1 in 12 and grade 2 in 1 patient after the main dose. In the bupivacaine group motor block was grade 0 in eight, grade 1 in 11 and grade 2 in 1 patient after the main dose. After the top-up motor block was grade 0 in two patients, grade 1 in 10 and grade 2 in eight patients in the ropivacaine group. After the top-up, in the bupivacaine group motor block was grade 0 in four, grade 1 in eight and grade 2 in six patients. No patient had grade 3 motor block at any stage during the study (table 4). Motor block, as assessed by the modified Bromage scale was not clinically different in the two groups.

CARDIOVASCULAR VARIABLES

Maternal systolic and diastolic arterial pressures, heart rate and fetal heart rate changed similarly in both groups. Hypotension occurred in six patients in each group and was categorized as mild in two, moderate in three and severe in one in each group. Transient fetal bradycardia was observed in three cases in the ropivacaine group and in three cases in the bupivacaine group. In no case was bradycardia considered indicative of severe fetal distress, and labour was allowed to progress.

MODE OF DELIVERY

In the ropivacaine group (n = 20) spontaneous vertex delivery occurred in 12 cases, assisted delivery in seven and Caesarean section was required in one case. The corresponding numbers in the bupivacaine group (n = 20) were 10, 7 and 3.

NEONATAL OUTCOME

An Apgar score of 7 or more at 1 min was recorded in 17 of 20 infants in the ropivacaine group and in 14 of 20 in the bupivacaine group. All neonates had a score of 9 or 10 at 5 min. In the ropivacaine group one neonate scored 1 at 1 min (cord around the neck at delivery), one scored 4 and one scored 6. In the bupivacaine group at 1 min, one neonate scored 3, one scored 5 and the remaining three scored 6.

Table 2  Median (range) onset and duration of pain relief and spread of sensory block in the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Main dose</th>
<th>Top-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ropivacaine (n = 20)</td>
<td>Bupivacaine (n = 20)</td>
</tr>
<tr>
<td>Onset time (min)</td>
<td>18 (7–27)</td>
<td>12 (3–24)*</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>52 (0–129)</td>
<td>64.5 (0–147)</td>
</tr>
<tr>
<td>Spread of sensory block</td>
<td>T9–S2</td>
<td>T9–S1</td>
</tr>
</tbody>
</table>

Table 3  Mean (range) quality of block in the two groups. No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Main dose</th>
<th>Top-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ropivacaine (n = 20)</td>
<td>Bupivacaine (n = 20)</td>
</tr>
<tr>
<td>VAS before main dose/top-up</td>
<td>84 (28–100)</td>
<td>69.5 (26–99)</td>
</tr>
<tr>
<td>VAS at 30–60 min</td>
<td>11.7 (0–94)</td>
<td>12.4 (0–85)</td>
</tr>
<tr>
<td>Overall good analgesia (n)</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>
Figure 1  Median (quartiles) VAS scores after the main dose of ropivacaine (A) or bupivacaine (B), and after top-up doses of ropivacaine (C) or bupivacaine (D). < 0 = Last VAS observation before dose.

Table 4  Degree of motor block in the two groups. No significant differences between groups

<table>
<thead>
<tr>
<th>Grade of motor block</th>
<th>Main dose</th>
<th>Top-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ropivacaine (n = 20)</td>
<td>Bupivacaine (n = 20)</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ADVERSE EVENTS
Immediate postpartum backache occurred in three patients in the ropivacaine group and five in the bupivacaine group. Urinary retention occurred in two patients in each group for which one patient in each group required catheterization for 24 h. Nausea or vomiting occurred in three patients in the ropivacaine group and in two in the bupivacaine group.

Discussion
An ideal local anaesthetic for extradural use in labour should produce effective and controllable sensory block of rapid onset and long duration but minimal motor block. It should have a high therapeutic index and minimal placental transfer. Bupivacaine has most of these characteristics but produces clinically significant motor block, particularly with repeated top-ups [11] and is toxic if accidentally injected i.v. [2].

Ropivacaine is produced as a single s-enantiomer and in animal and human volunteer studies was found to be less toxic than bupivacaine [6, 12]. It is of interest that in animal studies, S forms of bupivacaine and mepivacaine are less toxic and of longer duration than R forms.

We found that 0.5% ropivacaine or bupivacaine 10 ml followed by a top-up of 0.25% solution 10 ml produced effective, well tolerated pain relief in labour. The onset time of bupivacaine after the main dose was significantly shorter than that of ropivacaine; there were no other significant differences.
between ropivacaine and bupivacaine in duration or quality of sensory block. This is in agreement with other studies comparing extradural ropivacaine with bupivacaine in which no difference was found in onset, duration or maximum height of block with 0.5% and 0.75% concentrations of each drug [10, 11], or with 0.75% concentrations of each drug with adrenaline [13]. However, another group comparing 0.5% ropivacaine with 0.5% bupivacaine found that the sensory block of bupivacaine was slightly longer [14].

We were unable to demonstrate any difference in motor block between the groups and this conflicts with previous studies, although no previous studies involved top-ups. Two studies, using much higher doses of drug for surgery, found that extradural anaesthesia with ropivacaine produced a less intense motor block of slower onset and shorter duration than bupivacaine at the same concentration [10, 11]. However, in a study of 0.5% bupivacaine compared with 0.75% ropivacaine, there was no significant difference in motor block [16]. Other authors have compared 0.5% ropivacaine and bupivacaine and bupivacaine and found no difference in the onset or degree of motor block but found that the duration of motor block with bupivacaine was longer [14].

The Bromage scale is a qualitative method of assessing motor block and in this study the assessment of muscle groups by the modified Bromage scale might not have been expected to reveal quantitative differences in motor block between the two drugs at the doses given. A quantitative method of comparing motor block such as repeated maximal isometric contractions, as described by Axelsson [17], gives a more precise description of the degree and duration of motor block. With this method mean values of isometric muscle contractions after extradural block are calculated as a percentage of baseline values of muscle force. In a study using both the Bromage and Axelsson methods to measure motor block after extradural ropivacaine, full recovery of motor power, as judged by Bromage, occurred 1.5—2.5 h earlier than full recovery measured quantitatively [17]. Use of a quantitative method of assessment of motor block may have shown a difference in motor block between the two groups in our study.

Acknowledgements

Dr McCrae was in receipt of a research fellowship from Astra Pain Control AB and the study was supported by Astra Pain Control AB, Sodertalje, Sweden. We thank Jan Henriksson, Department of Statistics, Astra Pain Control.

References

13. Kerkamp HEM, Gielen MJM. Cardiovascular effects of epidural local anaesthetics: comparison of 0.75% bupivacaine and 0.75% ropivacaine, both with adrenaline. Anesthesia 1991; 46: 361—365.
15. Kerkamp HEM, Gielen MJM, Edstrom HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. Regional Anesthesia 1990; 15: 204—207.
16. Katz JA, Knarr D, Bridenbaugh PO. A double blind comparison of 0.5% bupivacaine and 0.75% ropivacaine administered epidurally in humans. Regional Anesthesia 1990; 15: 250—252.