Relative potencies of bupivacaine and ropivacaine for analgesia in labour

G. Capogna[1], D. Celleno[2], P. Fusco[3], G. Lyons[4] and M. Columb[5]

[1]Department of Anaesthesia and [3]Department of Obstetrics and Gynaecology, Fatebenefratelli General Hospital, Isola Tiberina 38, I-00186 Rome, Italy. [2]Department of Anaesthesia, Ospedale S. Giacomo in Augusta, v. Canova 29, I-00186 Rome, Italy. [4]St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK. [5]Intensive Care Unit, Withington Hospital, Nell Lane, Manchester M20 2LR, UK

We have used the technique of randomized, double-blind sequential allocation to compare the minimum local analgesic concentrations (MLAC) of epidural bupivacaine and ropivacaine for women in the first stage of labour. The test bolus was 20 ml of local anaesthetic solution. The concentration was determined by the response of the previous woman to a higher or lower concentration of local anaesthetic, according to up–down sequential allocation. Efficacy was assessed using a 100-mm visual analogue pain score (VAPS). The test solution had to achieve a VAPS of 10 mm or less to be judged effective. For bupivacaine, MLAC was 0.093 (95% CI 0.076–0.110)% w/v, and for ropivacaine, 0.156 (95% CI 0.136–0.176)%w/v ($P<0.0001$, 95% CI difference 0.036–0.090). The analgesic potency of ropivacaine was 0.60 (0.47–0.75) relative to bupivacaine. Claims for reduced toxicity and motor block must be considered with differences in analgesic potency in mind.

Studies performed in animals and human volunteers have shown that ropivacaine is less toxic than bupivacaine.[1–4] Clinical studies have shown that ropivacaine can provide pain relief in labour that is equivalent to bupivacaine[5] and it is also claimed that its use is associated with less motor block.[6] Ropivacaine may be less potent than bupivacaine,[7] and if this is the case, the validity of potential benefits regarding toxicity and motor block is in doubt until the relative therapeutic ratios have been established.

The aim of this study was to compare the relative analgesic potencies of these two local anaesthetics when given for pain relief in the first stage of labour. We did this by determining the minimum local analgesic concentration (MLAC), the median effective concentration (EC_{50}),[8] for each local anaesthetic.

Patients and methods

After obtaining approval from the Institutional Ethics Committee, we studied 87 healthy primipara, at more than 37 weeks' gestation, requesting epidural pain relief in labour at the Fatebenefratelli General Hospital, Rome, in a randomized, double-blind sequential allocation study. In order to standardize the progression of labour, only women with cervical dilatation of 2–5 cm inclusive, were enrolled.

Women requiring oxytocin augmentation, with presenting part below the ischial spines, and those scoring less than 30 (0–100 mm) on a visual analogue pain score (VAPS) were excluded. Women who had received opioid analgesics in the previous 6 h were also excluded.

While infusing i.v. Ringer's lactate solution, lumbar epidural analgesia was performed at either L2–3 or L3–4 with the woman in the left lateral position. Loss of resistance to saline was used, limiting injection to 2 ml to minimize dilution of local anaesthetic. The catheter was advanced 3 cm into the epidural space and then aspirated. For the purpose of the study, the test dose was omitted.

Each woman was allocated randomly to receive a freshly prepared syringe containing 20 ml of either bupivacaine (Marcain, Astra) or ropivacaine (Naropin, Astra), diluted with 0.9%w/v saline to achieve the desired concentration at room temperature. The concentration of the test solution in each individual syringe was determined by the response of the previous patient to the higher or lower concentration in her test syringe, according to up–down sequential allocation. The exception to this was the first woman in each group, for whom the starting concentration was 0.2%w/v.

Efficacy was assessed using a 100-mm VAPS (0='no pain' and 100='worst possible pain') at 0, 15 and 30 min after injection of the test solution. VAPS was assessed

Table 1 Patient and obstetric data (mean (SD or range) or median [interquartile range]). VAPS = Visual analogue pain score. No significant differences between groups (unpaired Student's *t* test or Mann–Whitney *U* test)

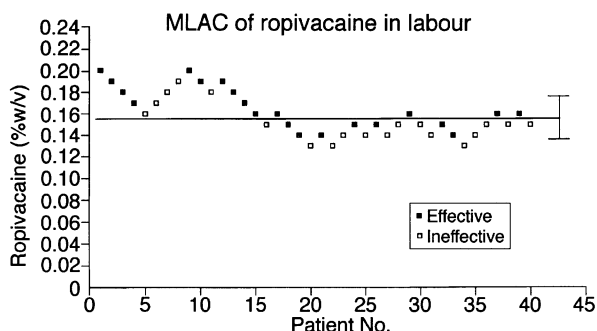|	Ropivacaine	Bupivacaine
Age (yr)	28.7 (22–43)	28.2 (23–37)
Height (cm)	166.1 (5.70)	167.5 (4.39)
Weight (kg)	72.4 (6.69)	72.8 (6.20)
Gestation (weeks)	40 [39–40]	40 [39–40]
Cervical dilatation (cm)	4 [3–4]	4 [3–5]
Station (cm above ischial spines)	1 [1–0]	1 [1–0]
VAPS (mm)	90 [80–100]	90 [84.5–95]

Fig 1 EC_{50} of ropivacaine, as determined by up–down sequential allocation. Error bars represent 95% confidence intervals. Testing interval was 0.1%w/v.
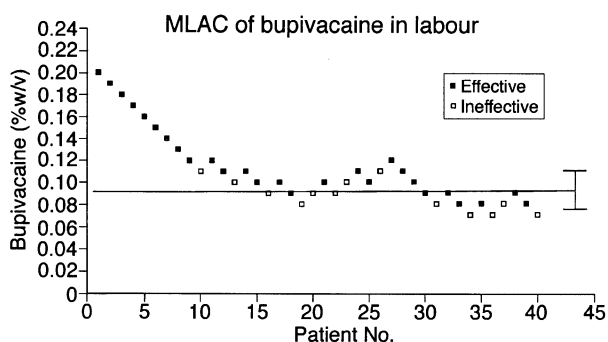

Fig 2 EC_{50} of bupivacaine, as determined by up–down sequential allocation. Error bars represent 95% confidence intervals. Testing interval was 0.1%w/v.

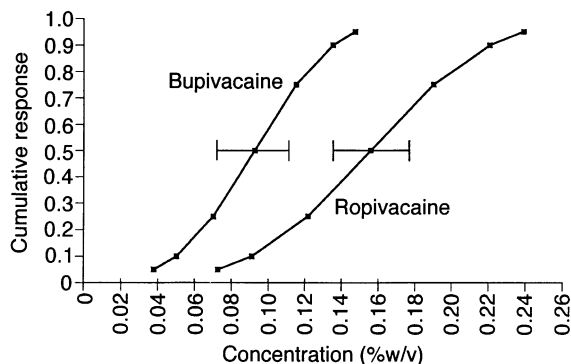**Fig 3** EC_{50} for ropivacaine and bupivacaine with 95% confidence intervals. Derived point estimates are plotted to demonstrate the concentration–response relationship.
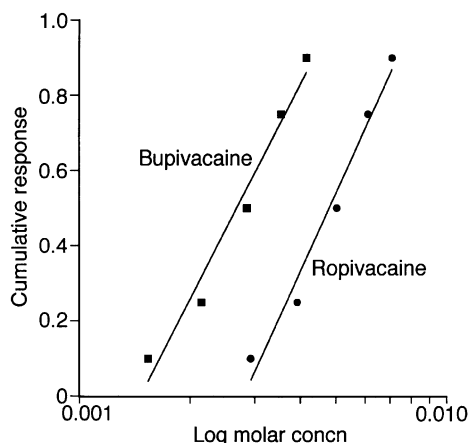

Fig 4 Log molar ropivacaine and bupivacaine concentration–response plots using derived point estimates.

during contraction, using a plastic ruler with the patient's side unmarked and the observer's side marked from 0 to 100 mm. A flowing cursor allowed the patient to give her score in a blinded manner.

There were three possible outcomes: *effective*—this required a VAPS of 10 mm or less, within 30 min, and directed a decrement of 0.01%w/v local anaesthetic solution for the next woman randomized to that group; *ineffective*—when the VAPS failed to reach 10 mm within 30 min, a rescue of 0.25%w/v bupivacaine 15 ml was given. If VAPS decreased to 10 mm or less within the next 30 min, a 0.01% w/v local anaesthetic increment was directed for the next woman randomized to that group; *repeat*—when the rescue bolus failed to achieve a VAPS of 10 mm or less, indicating failure of spread, this directed that the same concentration be repeated for the next woman randomized to that group.

Evidence of progression of labour beyond 6 cm cervical dilatation or descent of the fetal head below the ischial spines before an outcome was reached meant that the patient was withdrawn from the study and the concentration was repeated for the next woman.

Maternal heart rate, non-invasive arterial pressure and pulse oximetry, uterine contractions and fetal heart rate were monitored.

Patient and obstetric data were collected and are presented as mean (SD), median (interquartile range, IQR) and count, as appropriate, and analysed using Student's *t* test, Mann–Whitney *U* test and Fisher's exact test. Median effective concentrations were estimated from the up–down sequences using the formula of Dixon and Massey which enabled MLAC with 95% confidence intervals (CI) to be derived.[9] The sequences were also subjected to Wilcoxon and Litchfield probit regression analysis as a back-up or sensitivity test. Analyses were carried out using the following software: Microsoft Excel 5.0a for Windows, Statistical Package for the Social Sciences (SPSS) 6.1 for Windows, GraphPad Instat 2.05a for DOS and Pharmacologic Calculation System (PCS) 4.2 for DOS. Statistical significance was

defined for an overall α error at the 0.05 level and *P* values were two-sided.

Results

There were no significant differences in patient or obstetric characteristics between groups (Table 1). Eighty-seven women were enrolled (ropivacaine *n*= 44, bupivacaine *n*=43). Seven test syringes were repeated, leaving 40 women in each group for analysis.

The MLAC of ropivacaine was 0.156 (95% CI 0.136–0.176)%w/v; the MLAC of bupivacaine was 0.093 (95% CI 0.076–0.110)%w/v using the up–down formula of Dixon and Massey. This difference (95% CI difference 0.036–0.090) was significant (*P*<0.0001).

The sequences of effective and ineffective analgesia are shown in Figures 1 and 2. The concentration–response plots are shown in Figure 3. The relative potency of ropivacaine to bupivacaine was 0.60 (95% CI 0.47–0.75).

Molar MLAC (EC$_{50}$) was 5.02 (95% CI 4.37–5.66) mmol litre^{-1} for ropivacaine and 2.86 (95% CI 2.34–3.38) mmol litre^{-1} for bupivacaine. Molar potency ratio was 0.57 (95% CI 0.45–0.72). The log molar concentration–response plots are shown in Figure 4.

Discussion

Our study showed that, with regard to efficacy, ropivacaine was 60% as potent as bupivacaine in terms of %w/v when used for epidural pain relief in labour. Because determining potency in terms of mg ml^{-1} can under- or over-state true potency ratios, we also calculated potency ratio on a molar basis (57%). This was marginally reduced compared with %w/v potency because ropivacaine (propyl derivative) has one BCH$_2$ group less than bupivacaine (butyl derivative) and there are relatively more molecules of ropivacaine per gram weight.

Clinical studies comparing ropivacaine and bupivacaine in labour[5][10] have been performed using concentrations of bupivacaine that correspond to the flat upper part of the analgesic concentration–response curve.[11] It is now clear that this has also been true for ropivacaine. Concentrations of local anaesthetics on this part of the curve are likely to be at or beyond the EC$_{95}$ level. The predictable results of such studies that use concentrations found on the flat upper part of the curve are likely to show similarly effective analgesia among the local anaesthetics under evaluation. It should be appreciated that similarly effective analgesia does not imply that the concentrations compared are likely to produce equivalent effects at other points on the concentration–response curve. It should also be appreciated that concentrations above the EC$_{95}$ level are likely to produce a degree of motor block. Comparisons should be made at equi-analgesic concentrations rather than at presumed equivalent somatic sensory denervation, because the aim in labour is analgesia without complete deafferentation. A study performed comparing 0.1–0.3%w/v ropivacaine and 0.25%w/v bupivacaine showed less motor block with ropivacaine but more sustained analgesia with bupivacaine.[12] An explanation for this may simply be difference in potency.

Claims for reduced toxicity and motor block are made on the basis of weight for weight comparisons in animals and human volunteers. These claims are made on the assumption of equi-potency. If ropivacaine requires a 68% upward adjustment of dose to achieve equivalent analgesic potency with bupivacaine, the claims may no longer be valid.

In summary, we have shown that epidural ropivacaine was significantly less potent than bupivacaine by a factor of 0.4 when given to women in labour. Claims for reduced toxicity and motor block must be re-evaluated with analgesic efficacy in mind.

References

1 Reiz S, Haggmark S, Johansson G, Nath S. Cardiotoxicity of ropivacaine—a new amide local anaesthetic agent. *Acta Anaesthesiol Scand* 1989; **33**: 93–8

2 Moller R, Covino B. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. *Anesthesiology* 1990; **72**: 322–9

3 Santos AC, Arthur GR, Wlody D, de Armas P, Morishima HO, Finster M. Comparative systemic toxicity of ropivacaine and bupivacaine in pregnant and non-pregnant ewes. *Anesthesiology* 1995; **82**: 734–40

4 Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; **69**: 563–9

5 McCrae AF, McClure JH, Jozwiak H. Comparison of ropivacaine and bupivacaine in extradural analgesia for the relief of pain in labour. *Br J Anaesth* 1995; **74**: 261–5

6 Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *Br J Anaesth* 1991; **66**: 31–3

7 Reynolds F. Does the left hand know what the right hand is doing? An appraisal of single enantiomer local anesthetics. *Int J Obstet Anesth* 1997; **6**: 257–69

8 Capogna G, Celleno D, Lyons G, Columb MO, Fusco P. Minimum local analgesic concentration of extradural bupivacaine increases with progression of labour. *Br J Anaesth* 1998; **80**: 11–13

9 Dixon WJ, Massey FJ. *Introduction to Statistical Analysis*, 4th Edn. New York: McGraw-Hill, 1983: 428–39

10 Stienstra R, Jonker TA, Bourdrez PA, Kuijpers JC, van Kleef JW, Lundberg U. Ropivacaine 0.25% versus bupivacaine 0.25% for continuous epidural analgesia in labor: A double-blind comparison. *Anesth Analg* 1995; **80**: 285–9

11 Columb MO, Lyons G. Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. *Anesth Analg* 1995; **81**: 833–7

12 Zaric D, Per-Anders N, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers. *Reg Anesth* 1996; **21**: 14–25