Anesthesiology 2003; 99:1354–8

Relative Analgesic Potencies of Levobupivacaine and Ropivacaine for Epidural Analgesia in Labor

Linda S. Polley, M.D., Malachy O. Columb, F.R.C.A.,† Norah N. Naughton, M.D.,‡ Deborah S. Wagner, Pharm.D.,§ Cosmas J. M. van de Ven, M.D.,‖ Kathryn H. Goralski, M.D.#*

Background: **The minimum local analgesic concentration has been defined as the median effective local analgesic concentration (EC_{50}) in a 20-ml volume for epidural analgesia in the first stage of labor. The aim of this study was to assess the relative analgesic potencies of epidural levobupivacaine and ropivacaine by determination of their respective minimum local analgesic concentrations.**

Methods: **Parturients at 7 cm of cervical dilation or less who requested epidural analgesia were allocated to one of two groups in this double-blind, randomized, prospective study. After lumbar epidural catheter placement, 20 ml of the test solution was given: levobupivacaine (n = 35) or ropivacaine (n = 35). The concentration of local anesthetic was determined by the response of the previous patient in that group to a higher or lower concentration using up–down sequential allocation. Analgesic efficacy was assessed using 100-mm visual analog pain scale scores, with 10 mm or less within 30 min defined as effective. An effective result directed a 0.01% wt/vol decrement for the next patient. An ineffective result directed a 0.01% wt/vol increment.**

Results: **Of 105 women enrolled, 35 were excluded, leaving 70 for analysis. The minimum local analgesic concentration of levobupivacaine was 0.087% wt/vol (95% CI, 0.081–0.094%), and the minimum local analgesic concentration of ropivacaine was 0.089% wt/vol (95% CI, 0.075–0.103%). Levobupivacaine and ropivacaine were of similar potency with a ropivacaine: levobupivacaine potency ratio of 0.98 (95% CI, 0.80–1.20). No difference in motor effects was observed.**

Conclusions: **This study demonstrated that levobupivacaine and ropivacaine are of similar potency for epidural analgesia in the first stage of labor.**

EPIDURAL bupivacaine provides excellent analgesia for labor and delivery and remains the most widely used local anesthetic for obstetric analgesia. However, concerns regarding its potential for cardiovascular toxicity have prompted the search for alternative agents. Levobupivacaine and ropivacaine are relatively recently introduced amino amide local anesthetics that are structurally similar to bupivacaine. Both agents have been associated with less central nervous system and cardiac toxicity relative to bupivacaine when equal concentrations were compared.[1,2]

However, it is difficult to draw conclusions regarding analgesic efficacy and side effect profiles in the absence of information regarding the relative analgesic potencies of the two newer local anesthetics. To evaluate the pharmacodynamic contributions of various epidural analgesics, the minimum local analgesic concentration (MLAC) model was devised to determine the relative potencies of local anesthetics in the first stage of labor[3,4] and to estimate the local anesthetic–sparing potential of epidural opioids and adjuncts.[5–8] In a previous MLAC study, we found a 40% reduction in the analgesic potency of ropivacaine compared to bupivacaine.[4] In a separate MLAC study, Lyons *et al.*[9] found levobupivacaine to be equipotent to bupivacaine. Because the data are from two separate studies and the study of Lyons *et al.* had a very wide confidence interval (CI) for the potency ratio, it is difficult to draw conclusions regarding the relative potencies of the two newer drugs. This study was conducted to directly assess the relative potencies of epidural ropivacaine and levobupivacaine.

Materials and Methods

This research was conducted at the University of Michigan Health System, Ann Arbor, Michigan. After receipt of institutional review board approval and written informed patient consent, 105 parturients with American Society of Anesthesiologists physical status class I or II who requested epidural analgesia were enrolled. Participants had singleton pregnancies at greater than 36 weeks' gestation with vertex fetal presentation. All women were in active labor with cervical dilation of 3–7 cm at the time of catheter placement. Cervical dilation was manually assessed within 30 min before initiating the procedure. Detailed MLAC methodology has been previously described.[4,7]

Participants were allocated to one of two groups in a double-blind, randomized, prospective study design. The first group (n = 35) received 20 ml levobupivacaine (Chirocaine; Purdue Pharma L.P., Norwalk, CT) and the second group (n = 35) received 20 ml ropivacaine (Naropin; Astra USA, Inc., Westborough, MA). The concentration of local anesthetic received by a particular patient was determined by the response of the previous patient in that group to a higher or lower concentration, using an up–down sequential allocation technique. The test-

* Clinical Associate Professor, ‡ Clinical Associate Professor, Division of Obstetric Anesthesiology, ‖ Clinical Associate Professor, Division of Maternal-Fetal Medicine, # Resident, Department of Obstetrics and Gynecology, § Clinical Assistant Professor, University of Michigan Health System, Ann Arbor, Michigan. † Consultant in Anaesthesia and Intensive Medicine, South Manchester University Hospitals' Trust, Wythenshawe, United Kingdom.

Received from the Department of Anesthesiology, Women's Hospital, University of Michigan Health System, Ann Arbor, Michigan. Submitted for publication November 19, 2002. Accepted for publication March 12, 2003. Support was provided solely from institutional and/or departmental sources. Presented at the Annual Meeting of the American Society of Anesthesiologists, Orlando, Florida, October 12–16, 2002.

Address reprint requests to Dr. Polley: Department of Anesthesiology, 1500 East Medical Center Drive, F3900 Mott Children's Hospital, Ann Arbor, Michigan 48109-0211. Address electronic mail to: lpolley@umich.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Table 1. Demographic and Obstetric Data

	Levobupivacaine	Ropivacaine
Age, yr	29 (6.0)	29 (5.9)
Height, cm	166 (8.4)	165 (6.7)
Weight, kg	86 (15.2)	90 (18.6)
Gestation, wk	40 (1.3)	40 (1.4)
Cervical dilatation, cm	4 [4, 5]	5 [4, 6]
Nulliparous	19/35	21/35
Oxytocin	19/35	16/35
Initial VAPS, mm	76 [68, 86]	80 [65, 89]

Results are expressed as mean (SD), median [interquartile range], and count, as appropriate.

VAPS = visual analog pain score.

ing interval was 0.01% wt/vol for each drug. The first patient in each group received 0.10% wt/vol levobupivacaine or ropivacaine based on an estimate of MLAC from a previous study.[4] Maternal and fetal hemodynamic data were recorded at 5-min intervals.

The efficacy of the study drug was assessed using 100-mm visual analog pain scale (VAPS) scores, where 0 represented no pain and 100 represented the worst possible pain, at 10-min intervals for the first 30 min after bolus injection. A VAPS of 10 mm or less was defined as effective. Three outcomes were considered:

1. *Effective*: VAPS of 10 mm or less during contractions within 30 min after injection. A result defined as effective directed a 0.01% wt/vol decrement for the next patient in that group.

2. *Ineffective*: VAPS of greater than 10 mm because of pain that responded to rescue with a 12 ml-bolus of 0.25% wt/vol of the same local anesthetic. A result defined as ineffective directed a 0.01% wt/vol increment for the next patient in that group.

3. *Reject*: VAPS of greater than 10 mm because of pain not responsive to rescue. A result defined as a reject directed that the same concentration be repeated for the next patient randomized to that group.

At 30 min, participants not defined as having effective analgesia were given the rescue bolus. Those unresponsive to rescue were designated as rejects. Parturients who entered the second stage of labor (defined as complete cervical dilation) during the study were also excluded.

In addition to VAPS assessment, other data collected at 10-min intervals included sensory level and degree of motor blockade. Sensory level was determined by perceived temperature difference to alcohol swab. Motor block was assessed bilaterally at 10-min intervals using the modified Bromage scale. To determine the duration of effective analgesia, women reporting a VAPS of 10 mm or less received no additional medication until their request.

Fetal Assessment

A perinatologist blinded to the study group allocation reviewed fetal heart rate tracings obtained during the first hour of the study using the National Institutes of Health research guidelines for interpretation of electronic fetal heart rate monitoring.[10]

Table 2. Maternal and Fetal Hemodynamic Data

	Levobupivacaine		Ropivacaine	
	Mean	SD	Mean	SD
Baseline maternal MAP, mmHg	94	13.2	94	12.1
Lowest maternal MAP, mmHg	82	9.0	85	10.3
Overall maternal HR, beats/min	83	10.3	85	10.3
Overall maternal Spo_2, %	98	1.4	98	1.6
Baseline fetal HR, beats/min	136	12.0	138	18.4
Overall fetal HR, beats/min	136	8.7	136	11.2
Lowest fetal HR, beats/min	127	12.1	124	14.8

Results are expressed as mean ± SD.

HR = heart rate; MAP = mean arterial pressure; Spo_2 = oxygen saturation measured by pulse oximetry.

Statistical Analysis

Demographic and obstetric data were collected and are presented as mean (SD), median (interquartile range), and count as appropriate. Means (SDs) were analyzed using unpaired Student *t* or Welch *t* tests for differing variances, medians (interquartile ranges) by Mann–Whitney *U* test, and counts or proportions by Fisher exact test. The median effective concentrations were estimated from the up–down sequences using the method of Dixon and Massey,[11] which enabled MLACs with 95% CIs to be derived. The sequences were also subjected to Wilcoxon and Litchfield probit regression analyses as backup or sensitivity tests. In addition, an intention-to-treat analysis using probit regression was performed on all randomized subjects, with reject outcomes redefined as ineffective. Analyses were performed using the following software: Excel 2000 (Microsoft Corp., Redmond, VA), Number Crunching Statistical System 2000 (NCSS Inc., Kaysville, UT), GraphPad Prism 3.02 (GraphPad Software Inc., San Diego, CA), and Pharmacological Calculation System 4.2 (Microcomputer Specialists, Wynewood, PA). Statistical significance was defined for an overall α error at the 0.05 level. All *P* values were two sided.

Table 3. Distribution of Excluded Patients

% wt/vol	Levobupivacaine	Ropivacaine
0.11		1(A)
0.10	2(A) 1(B) 1(C)	1(A)
0.09	4(A) 1(B) 3(C) 1(E)	1(A) 1(C) 1(F)
0.08	5(A) 2(B) 2(C) 1(D) 3(E)	1(A)
0.07	2(A) 1(B)	

A = visual analog pain score > 10 mm because of pain that fails to respond to rescue, concentration repeated; B = protocol violation, concentration repeated; C = second stage of labor before study completion, concentration repeated; D = intravascular epidural catheter, concentration repeated; E = patient withdrew from study, concentration repeated; F = fetal heart rate deceleration.

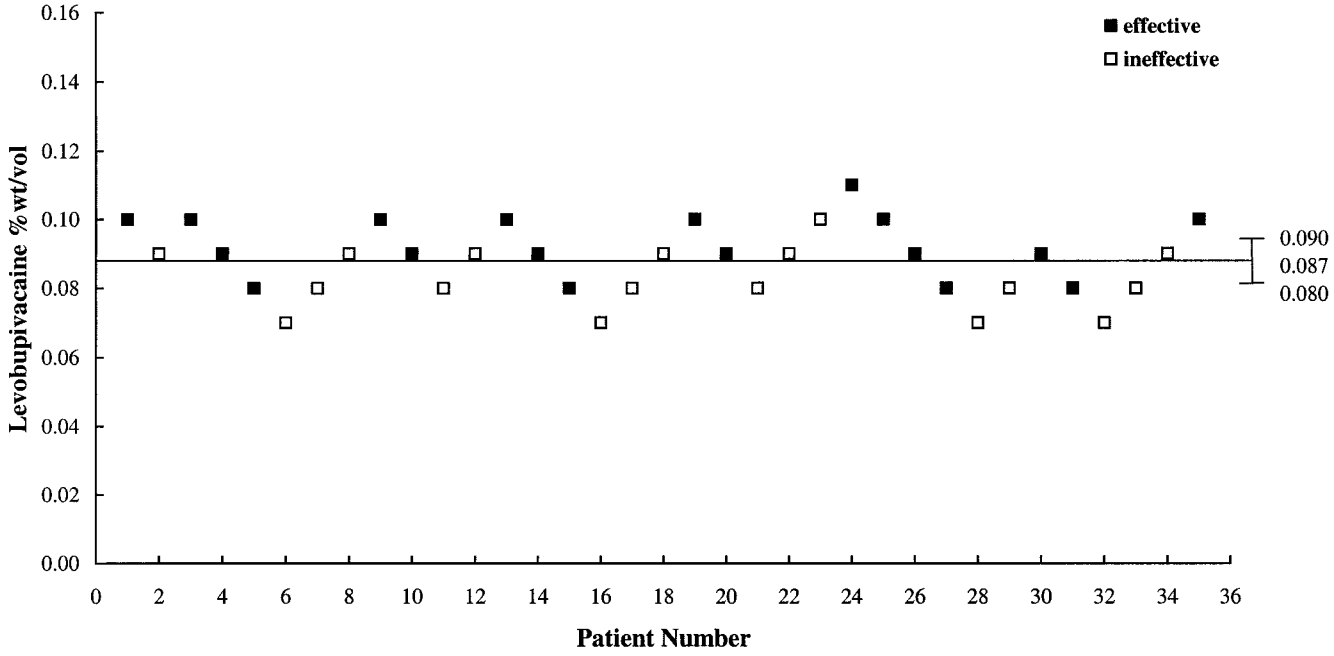

Fig. 1. The median effective local analgesic concentration of levobupivacaine as determined by the technique of up–down sequential allocation. The minimum local analgesic concentration (MLAC) is 0.087% wt/vol. *Error bars* represent 95% CIs. The testing interval was 0.01% wt/vol.

Results

Demographic and obstetric characteristics were similar for both groups (table 1). There were no significant maternal or fetal hemodynamic differences between the groups (table 2). The study was discontinued in one patient in the ropivacaine group for fetal bradycardia secondary to umbilical cord prolapse.

Of the 64 women enrolled in the levobupivacaine group, 29 were excluded (table 3), leaving 35 for analysis. The sequences of effective and ineffective analgesia are shown in figure 1. The MLAC of levobupivacaine in the first stage of labor was 0.087% wt/vol (95% CI, 0.08–0.09%) using the formula of Dixon and Massey and was 0.086% wt/vol (95% CI, 0.08–0.09%) using probit regression analysis as a backup sensitivity test.

Of the 41 women enrolled in the ropivacaine group, 6 were excluded (table 3), leaving 35 for analysis. The sequences of effective and ineffective analgesia are shown in figure 2. The MLAC of ropivacaine in the first stage of labor was 0.089% wt/vol (95% CI, 0.08–0.10%) using the formula of Dixon and Massey and probit regression analysis as a backup sensitivity test.

Levobupivacaine and ropivacaine seem to have a similar potency, with a ropivacaine:levobupivacaine potency ratio of 0.98 (95% CI, 0.80–1.20) in this study.

Block Characteristics

There was no difference between the study groups in the time to onset of the block, which was defined as the time to a VAPS of 10 mm or less in the effective groups

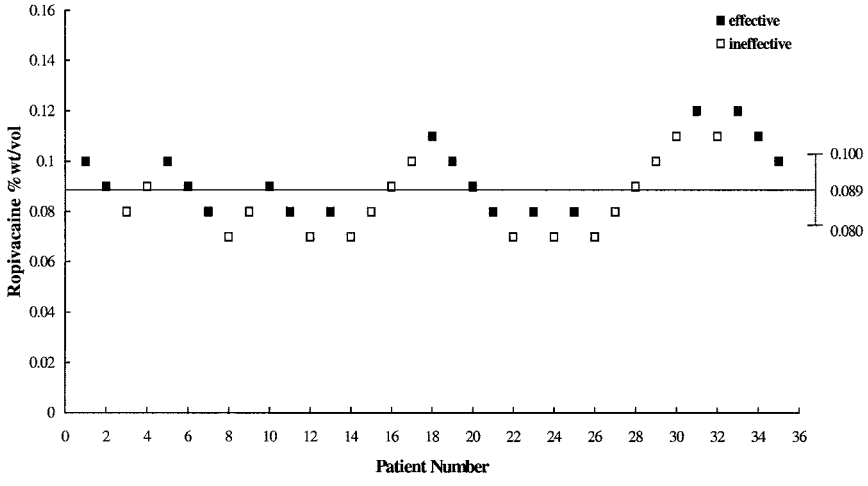

Fig. 2. The median effective local analgesic concentration of ropivacaine as determined by the technique of up–down sequential allocation. The minimum local analgesic concentration (MLAC) is 0.089% wt/vol. *Error bars* represent 95% CIs. The testing interval was 0.01% wt/vol.

Table 4. Block Characteristics

	Levobupivacaine	Ropivacaine
Onset time, min	22 (7.5)	23 (9.2)
Dermatomal level	T7 [T8, T5]	T7 [T9, T6]
Offset time, min	63 (17.9)	75 (24.4)
Bromage score	0 [0, 0]	0 [0, 0]

Results are expressed as mean (SD) and median [interquartile range].

(table 4). There was no difference in the cephalad level of dermatomal spread, block duration, or motor block as assessed by the modified Bromage scale.

Fetal Assessment

Perinatologist review of continuous fetal heart rate tracings did not reveal significant differences between the study groups. One patient in the ropivacaine group underwent an immediate cesarean section for fetal bradycardia secondary to umbilical cord prolapse.

Discussion

The MLACs of epidural levobupivacaine and ropivacaine have not been previously compared; however, both local anesthetics have been compared to bupivacaine in three separate studies using MLAC methodology. The analgesic potency of ropivacaine was found to be 40% less than that of racemic bupivacaine, with a ropivacaine:bupivacaine potency ratio of 0.6 (95% CI, 0.49–0.74).[4,12] Levobupivacaine and racemic bupivacaine were found by Lyons *et al.*[9] to have similar analgesic potencies, with a levobupivacaine:bupivacaine potency ratio of 0.98 (95% CI, 0.67–1.41). Taken together, these previous investigations have led to the assumption that levobupivacaine is more potent than ropivacaine. Our findings that levobupivacaine and ropivacaine were of similar potency in this study with a ropivacaine:levobupivacaine potency ratio of 0.98 (95% CI, 0.80–1.20) was surprising. These apparently discordant results are likely best explained by the wide CI in the study by Lyons *et al.* of levobupivacaine *versus* bupivacaine. In addition, there is always uncertainty when drawing conclusions from data in separate studies.

Previous studies compared 0.75% epidural levobupivacaine with 0.75% racemic bupivacaine for lower abdominal surgery[13] and 0.25% of each local anesthetic for labor analgesia.[14] Not surprisingly, the investigators did not find significant differences in the quality of analgesia, sensory block, or motor block. Supramaximal concentrations correspond to the upper, flatter portion of the dose–response curve, where anesthetic success is predictable and expected and potency differences are obscured. These results are not applicable to the markedly lower concentrations in current use for labor analgesia.

Table 5. Logistic Regression Analysis

Variable	*P* Value
Concentration	0.0011
Drug	0.2635

Table 6. Probit Regression Analysis

	EC_{50}	CI
Levobupivacaine	0.09%	0.09–0.10
Ropivacaine	0.09%	0.08–0.11

CI = confidence interval.

Intention-to-treat Analysis

Because of the marked disparity between the number of excluded patients in each study group, we also subjected our results to intention-to-treat analysis. For this purpose, all excluded patients were considered unresponsive to treatment. Logistic regression analysis showed no material change to results. The only significant variable was concentration of local anesthetic (table 5).

Probit regression analysis also demonstrates little difference between the drugs (table 6). The E_{50} estimates are higher as expected because of the great increase in the number of treatment failures after the addition of excluded parturients.

Molecular Expression and Units

Local anesthetic concentrations are described in units of wt/vol percent or milligrams per milliliter. It is important to note that the weight in milligrams may refer to the combination hydrate, salt, or base. Bupivacaine and ropivacaine are expressed as hydrochlorides. The 0.25% concentration yields 2.5 mg/ml bupivacaine hydrochloride or ropivacaine hydrochloride, respectively. As previously reported,[9] the more recent addition, levobupivacaine, was subjected to a change in expressed formulation by drug licensing authorities, which mandated labeling as milligrams of active moiety only.[15] Therefore, 0.25% levobupivacaine contains 2.5 mg/ml free base or 13% more active moiety than racemic bupivacaine, which is not subject to the new guidelines. In addition, the lower molecular weight of ropivacaine implies that there are 4% more molecules compared to racemic bupivacaine. To avoid confusion, the Système Internationale d' Unitès (SI system) recommends the use of molar concentrations that express the concentration in terms of the molecular weight of the base. The SI sytem is in widespread use in many countries, not including the United States. The molar concentrations of 2.86 mM and 3.01 mM for ropivacaine and levobupivacaine, respectively, shift the potency ratio to 1.05 for ropivacaine:levobupivacaine. This suggests that ropivacaine may be 5% more potent, but again, this difference is not clinically significant.

We have compared the commercially available prepa-

rations of the two local anesthetics to obtain clinically relevant results. Similar potencies were found for both ropivacaine and levobupivacaine under the conditions of this study.

References

1. Santos AC, DeArmas PI: Systemic toxicity of levobupivacaine, bupivacaine, and ropivacaine during continuous intravenous infusion to nonpregnant and pregnant ewes. ANESTHESIOLOGY 2001; 95:1256–64
2. Chang D-HT, Ladd LA, Wilson KA, Gelgor L, Mather LE: Tolerability of large-dose intravenous levobupivacaine in sheep. Anesth Analg 2000; 91:671–9
3. Columb MO, Lyons G: Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. Anesth Analg 1995; 81:833–7
4. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ: Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: Implications for therapeutic indexes. ANESTHESIOLOGY 1999; 90:944–50
5. Polley LS, Columb MO, Lyons G, Nair SA: The effect of epidural fentanyl on the minimum local analgesic of epidural chloroprocaine in labor. Anesth Analg 1996; 83:987–90
6. Lyons G, Columb MO, Hawthorne L, Dresner M: Extradural pain relief in labour: Bupivacaine sparing by extradural fentanyl is dose dependent. Br J Anaesth 1997; 78:493–7
7. Polley LS, Columb MO, Wagner DS, Naughton NN: Dose dependent reduction of the minimum local analgesic concentration (MLAC) of bupivacaine by sufentanil for epidural analgesia in labor. ANESTHESIOLOGY 1998; 89:626–32
8. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJM: Effect of epidural epinephrine on the minimum local analgesic concentration of epidural bupivacaine in labor. ANESTHESIOLOGY 2002; 96:1123–8
9. Lyons G, Columb MO, Wilson RC, Johnson RV: Epidural pain relief in labour: Potencies of levobupivacaine and racemic bupivacaine. Br J Anaesth 1998; 81:899–901
10. Parer JT: National Institute of Child Health and Human Development Research Planning Workshop. Electronic fetal heart rate monitoring: Research guidelines for interpretation. Am J Obstet Gynecol 1997; 177:1385–90
11. Dixon WJ, Massey FJ: Introduction to Statistical Analysis, 4th edition. New York, McGraw-Hill, 1983
12. Capogna G, Celleno D, Fusco P, Lyons G, Columb M: Relative potencies of bupivacaine and ropivacaine for analgesia in labour. Br J Anaesth 1999; 82:371–3
13. Kopacz DJ, Allen HW, Thompson GE: A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg 2000; 90:642–8
14. Burke D, Henderson DJ, Simpson AM, Faccenda KA, Morrison LMM, McGrady EM, McLeod GA, Bannister J: Comparison of 0.25% S(-)-bupivacaine with 0.25% RS-bupivacaine for epidural analgesia in labour. Br J Anaesth 1999; 83:750–5
15. Lyons G: Pharmacology of local anesthetics, Textbook of Obstetric Anesthesia. Edited by Birnbach DJ, Gatt SP, Datta S. Philadelphia, Churchill Livingstone, 2000, pp 84–5