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Dose–Response Study of Epidural Ropivacaine for Labor Analgesia

Bee Beng Lee, M.B.B.S., F.A.N.Z.C.A., Warwick D. Ngan Kee, M.D., F.A.N.Z.C.A.,† Eliza L. Y. Wong, M.P.H.,‡ Justina Y. W. Liu, B.S.N.‡*

Background: **Ropivacaine has been introduced for use in epidural analgesia in labor. However, there have been few formal dose–response studies of ropivacaine in this setting.**

Methods: **The authors performed a prospective, randomized, double-blind study examining the effectiveness of five different doses of ropivacaine (10, 20, 30, 40, and 50 mg) administered epidurally in a volume of 10 ml to establish analgesia in 66 parturients who were in active labor with cervical dilatation less than 4 cm. A dose was considered effective when the visual analog scale pain score decreased by 50% or more from baseline.**

Results: **A sigmoid dose–response curve and a probit log dose–response plot (linear regression coefficient, r = 0.84; coefficient of determination, $r^2 = 0.71$) were obtained. The ED_{50} (median effective dose) obtained based on the maximum likelihood estimation was 18.4 mg (95% confidence interval, 13.4–25.4 mg). Time to onset of analgesia, duration of analgesia, time to two-segment regression of sensory block level, and incidence of motor block were not affected by the dosage of ropivacaine administered ($P = 0.93$, 0.12, 0.55, and 0.39, respectively). However, the upper level of sensory block was dose-related ($P < 0.01$).**

Conclusion: **In a traditional dose–response study, the ED_{50} of ropivacaine required to initiate epidural analgesia in early labor was found to be 18.4 mg (95% confidence interval, 13.4–25.4 mg).**

ROPIVACAINE is a long-acting amide local anesthetic, related structurally to bupivacaine, that has been introduced for use in epidural analgesia in labor. Currently, the optimum dosage regimen for ropivacaine in this setting has not been determined, and recommended initial doses have ranged from 20 to 40 mg.[1–7] Because there have been few formal investigations of dose requirements for epidural ropivacaine, we performed a prospective, randomized, double-blind study to determine the dose–response of ropivacaine to establish epidural analgesia in early labor.

Materials and Methods

This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China. Written informed consent was obtained from all patients. We planned to recruit 75 women with American Society of Anesthesiologists physical status I and II who requested epidural analgesia in early labor. Patients were eligible for recruitment if they had term singleton pregnancies with cephalic presentation and were in established labor with cervical dilation less than 4 cm. Patients were excluded if they had preeclampsia, had received parenteral opioids, or had any contraindication to epidural analgesia.

Patients were instructed on the use of a 100-mm visual analog scale (VAS) ruler for assessment of pain (0 = no pain, 100 = worst pain imaginable), and a baseline pain score was recorded at the peak of a uterine contraction. After intravenous preload of 500 ml lactated Ringer's solution, patients were turned to the left lateral position. The epidural space was located at the L2–L3 or L3–L4 vertebral interspace using a loss-of-resistance technique with a 16- or 18-gauge Tuohy needle after skin infiltration with lidocaine. After its patency was checked by flushing with saline, an epidural catheter was inserted 4 cm into the epidural space and secured. Patients were then turned supine with lateral uterine displacement using a wedged pillow. Patients were randomly allocated, by drawing of shuffled coded sealed envelopes, to receive one of five doses of ropivacaine diluted to 10 ml with saline: 10, 20, 30, 40, or 50 mg (n = 15 per group). Each dose was prepared by an anesthesiologist who was not involved with patient assessments. Initially, 3 ml of the solution was injected as a test dose. Three minutes later, after excluding signs of spinal block, the remainder of the dose was injected over 30 s.

We collected the following data at 5-min intervals for 30 min, then at 10-min intervals until patients requested further analgesia: VAS pain score at the peak of a uterine contraction; upper dermatomal level of sensory block assessed by loss of discrimination to cold using ice; motor block according to a modified Bromage scale (0 = able to lift extended leg at the hip, 1 = able to flex the knee but not lift extended leg, 2 = able to move the foot only, 3 = unable to move even the foot); maternal pulse rate and arterial blood pressure; and the presence and severity of sedation, nausea or vomiting, and pruritus, each scored on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe and requiring intervention). A decrease in maternal systolic arterial pressure below 20% of baseline indicated the need for treatment with intravenous fluid and ephedrine in 3-mg increments. Fetal heart rate and uterine contractions were monitored using continuous external cardiotocodynamometry. When

* Adjunct Assistant Professor, † Associate Professor, ‡ Research Nurse.

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Address reprint requests to Dr. Lee: Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, Shatin, Hong Kong, China. Address electronic mail to: bblee@cuhk.edu.hk.

Table 1. Patient Characteristics

Group	10 mg	20 mg	30 mg	40 mg	50 mg	*P* Value
Age (yr)	31.2 (3.2)	29.4 (4.7)	30.1 (5.6)	27.3 (4.5)	28.7 (5.2)	0.42
Weight (kg)	68.0 (6.7)	63.8 (8.3)	69.2 (13.2)	67.4 (9.8)	68.7 (7.5)	0.57
Height (cm)	156.7 (3.4)	154.4 (5.8)	155.4 (4.8)	158.1 (6.0)	158.4 (4.7)	0.19
Gestation (weeks)	39.4 (1.5)	40.1 (1.7)	39.9 (1.2)	40.1 (1.7)	39.8 (1.6)	0.83
Parity (n)	P0 = 6	P0 = 12	P0 = 12	P0 = 15	P0 = 12	
	P1 = 0	P1 = 3	P1 = 2	P1 = 0	P1 = 3	0.31
	P2 = 0	P3 = 0	P2 = 1	P2 = 0	P2 = 0	
Cervical dilatation (cm)*	2 (1–3)	2 (1–3)	2 (0–3)	2 (1–3)	2 (1–2)	0.41
Oxytocin use (n)	3 (50%)	5 (33%)	7 (47%)	9 (60%)	7 (47%)	0.71
Baseline VAS pain score (mm)†	78.8 (71.1, 86.6)	77.5 (70.0, 86.0)	80.0 (70.0, 95.0)	80.0 (70.0, 90.0)	85.0 (80.0, 90.0)	0.56

All values are mean (SD) except: * median (range), † median (interquartile range).
VAS = visual analog scale.

patients requested further analgesia, they were treated with epidural "topups" of additional local anesthetic and commenced on a continuous epidural infusion of a dilute local anesthetic–opioid solution according to our usual labor ward practice, and the study was terminated. If the pain score did not decrease to at least 50% of the baseline value within 30 min of injection of the study dose, rescue analgesia in 5-ml aliquots of 0.25% ropivacaine was given epidurally to a maximum of two doses over 20 min. If analgesia was still inadequate after all the above, the epidural was declared nonfunctional and was resited. The patient would then be excluded from the study.

Patients were questioned the following day and requested to grade their satisfaction with their labor epidural analgesia according to a 0–10-point numerical scale (0 = totally unsatisfied, 10 = most satisfied). Attending midwives were also similarly interviewed to obtain their satisfaction gradings.

Statistical Analysis

Patient characteristics are presented as mean and SD, or median and range/interquartile range where appropriate, and were compared for homogeneity of randomization. An effective dose ("success") was defined as a dose that produced a reduction in pain score to 50% or less of baseline within 30 min of epidural drug injection. For each successful response, the onset time of analgesia was defined as the time from injection of drug[8] to reduction in pain score by 50%. We defined the duration of analgesia as the time from drug injection until return of pain score to 50% of baseline. In addition, we also recorded the time to the patient's first request for analgesia after the study dose.[8–10]

Data for successful responses for each dosage category were used to plot a sigmoid dose–response curve and a probit-log dose–response relation. With probit transformation, the log dose–response sigmoid curve is transformed to a straight line when the ordinates are measured on a scale linear in probits instead of in percentages.[11] Probit regression was performed, and the coefficients were estimated using the maximum likelihood estimation, and interpolation was performed to obtain the ED_{50} (median effective dose) and ED_{95} (95% effective dose).[11]

Time to onset of analgesia, duration of analgesia, upper sensory level, time to two-segment regression of sensory block (as observed during the latter half of the data collection period when the block was regressing), motor block, and maternal and midwife satisfaction scores were compared. Hypotension was defined as a decrease in systolic arterial pressure below 20% of baseline, when correction measures were instituted as described. For analysis of side effects, an overall or "summed" score for each parameter was calculated by adding the individual severity scores for each patient, thereby taking into account both the frequency and severity of the side effect concerned.

Parametric data were analyzed using analysis of variance, and nonparametric data were analyzed with the Kruskal–Wallis test or chi-square analysis using SPSS 8.0 (Chicago, IL). Serial data (pain scores, blood pressure, pulse rate, fetal heart rate) were analyzed using linear longitudinal mixed-model analysis[12] for the effect of the dose of epidural ropivacaine on these parameters and their trends across time. S-Plus version 4.5 (Seattle, WA) was used to perform these analyses, adjusting for potential confounding factors. $P \leq 0.05$ was considered statistically significant.

Results

Sixty-six patients completed the study. Recruitment to the 10-mg group was stopped after six cases after interim analysis showed that analgesia was inadequate in all of these patients. Fifteen patients were recruited into each of the four remaining dose groups. No epidural catheter required resiting. Data from the 10-mg group were omitted from the analyses of characteristics of epidural drug effects and satisfaction scores.

Patient demographics, obstetric characteristics, and baseline pain scores were similar among groups (table

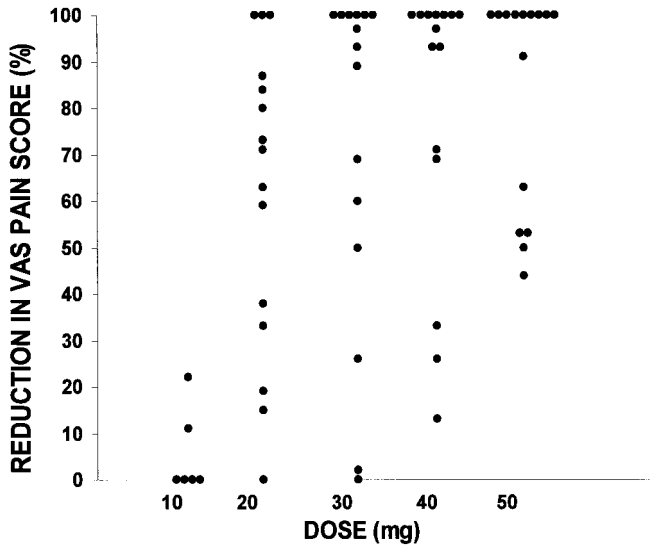

Fig. 1. Percentage reduction in visual analog scale (VAS) pain score for individual patients, with each point representing a patient.

1). The percentage reduction in VAS pain score for each patient, arranged according to dose group, is depicted in figure 1. Analgesic success rates for the different doses are shown in table 2, and the dose–response curve constructed from these data is shown in figure 2 (derivation of the equation is given in Appendix 1). A linear regression was fitted to the probit-log dose–response plot, with a regression coefficient (r) of 0.84 and a coefficient of determination (r^2) of 0.71 (fig. 3). Based on these results and using the maximum likelihood estimation, the calculated ED_{50} was 18.4 mg (95% confidence interval [CI], 13.4–25.4 mg), and the ED_{95} was 55.9 mg (95% CI, 35.3–88.5 mg). The estimated ED_{95} dose falls outside the dose range of our study and is an extrapolated point on both dose–response plots.

There was no significant effect of dosage on the time to onset of analgesia ($P = 0.93$), duration of analgesia ($P = 0.12$), and time to two-segment regression of sensory block level ($P = 0.55$) (table 3). Although the duration of analgesia was not significantly dose-related, there was a trend toward a longer duration of analgesia with larger epidural doses in this study. The incidence of motor block was small and similar among groups. However, dosage had a significant effect on the upper level of sensory block ($P < 0.01$). The time for pain scores to return to 50% of baseline was similar to the time to patients' first request for subsequent analgesia.

Analysis of serial measurements showed that the dose of ropivacaine used was significantly associated with pain scores: larger doses were associated with lower pain scores ($P < 0.01$), and there was a significant trend across time ($P < 0.001$). Dose was not associated with changes in maternal blood pressure or pulse rate. The incidence of hypotension was similar among groups ($P = 0.61$) and ranged from 7 to 20%. No adverse fetal heart rate changes were observed. Nausea and vomiting, sedation, and pruritus were infrequent (summed or overall scores of 0–2) and similar among groups. There was also no difference in maternal or midwife satisfaction scores (median, 8–9; range, 7–10 for both).

Discussion

Regional analgesic techniques, whether lumbar epidural or combined spinal–epidural, are the most effective methods of providing analgesia in labor. However, although dose–response studies have been published for intrathecal lipophilic opioids for labor analgesia,[8,13–16] few data are available for epidural ropivacaine and other local anesthetics. In our dose–response study, we included doses of ropivacaine from 10 to 50 mg, which is the range previously used as epidural loading doses in obstetric labor analgesia.[1–7] Using this range, our calculated value for ED_{50} indicates that for parturients in early labor, a dose of 18.4 mg (95% CI, 13.4–25.4 mg) should provide analgesia in 50% of patients. Although we also calculated the ED_{95}, the resultant value of 55.9 mg (95% CI, 35.3–88.5 mg) was outside the range of doses we studied and was obtained by extrapolation; this dose is very large and should be interpreted with caution.

Other dose-finding studies of epidural ropivacaine for labor analgesia that used different methodology to ours have been reported previously. In related studies, Polley *et al.*[10] and Capogna *et al.*[17] estimated the minimal local analgesic concentration of ropivacaine given in a 20-ml volume using the up–down sequential allocation method of Dixon and Massey,[18] and obtained values of 22 mg (95% CI, 20.0–24.4 mg) and 31.2 mg (95% CI, 27.2–35.2 mg), respectively. In a study by Beilin *et al.*,[9] using a sequential study design, epidural ropivacaine in concentrations of 0.10, 0.15, or 0.20% was given in a volume of 13 ml, and the ED_{50} equivalent obtained was in the range of 27–36 mg. In comparison, our value for ED_{50} of 18.4 mg (95% CI, 13.4–25.4 mg) is at the lower end of the range of values reported in these other studies.

The difference in results among these studies can be accounted for by several factors, including differences in

Table 2. Success Rates for Analgesia

Group	10 mg (n = 6)	20 mg (n = 15)	30 mg (n = 15)	40 mg (n = 15)	50 mg (n = 15)	*P* Value
Success (%)	0/6 (0)	10/15 (66.7)	12/15 (80.0)	12/15 (80.0)	14/15 (93.3)	< 0.01

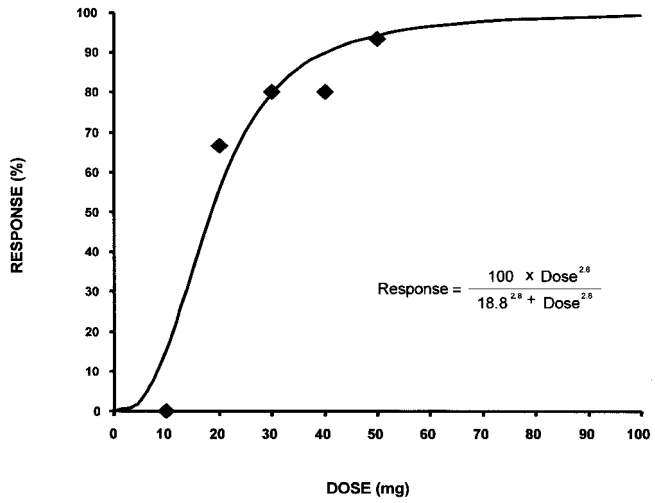

Fig. 2. Sigmoid dose–response curve for the five different doses of epidural ropivacaine given in a 10-ml volume. The sigmoid curve was obtained by fitting the data to a sigmoid E_{max} curve (see Appendix 1 for derivation of the equation).

study design and methodology, differences in patient recruitment criteria, and differences in the definition of adequate analgesia. We have used a traditional dose–response study design; in comparison, Polley *et al.*[10] and Capogna *et al.*[17] used the up–down sequential allocation technique of Dixon and Massey,[18] and Beilin *et al.*[9] used a sequential study design. In our study, we gave the doses in a standardized 10-ml volume; in comparison, Polley *et al.*[10] and Capogna *et al.*[17] gave the doses in a volume of 20 ml, whereas Beilin *et al.*[9] used 13 ml. These differences in injectate volume may have contributed to differences in results of these studies, although the exact effect is uncertain as the literature contains conflicting data regarding the relative effects of dose, volume, and

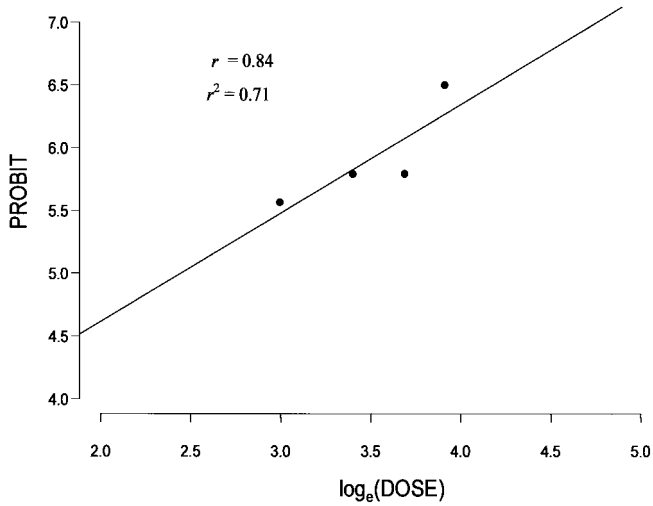

Fig. 3. Probit-log dose–response plot. A linear regression line was fitted using the method of Finney,[11] and ED_{50} and ED_{95} values were calculated using the maximum likelihood estimation. ED_{50} = 18.4 mg (95% confidence interval, 13.4–25.4 mg). ED_{95} = 55.9 mg (95% confidence interval, 35.3–88.5 mg). r = 0.84, r^2 = 0.71.

concentration on the extent or spread of epidurally administered local anesthetics. In our study, we kept the volume of injectate constant and found that the upper sensory level was directly related to the dose and concentration of ropivacaine contained in the epidural injectate, an effect that has previously been demonstrated with bupivacaine.[19,20]

Other differences among these studies include recruitment criteria with respect to cervical dilatation, parity, and augmentation of labor. We recruited women with cervical dilation of less than 4 cm who had not received parenteral opioids. In comparison, Polley *et al.*[10] recruited women with cervical dilation up to 7 cm, while Capogna *et al.*[17] included only women with cervical dilatation of 2–5 cm. The degree of cervical dilation is a potential confounding factor in the assessment of labor pain as pain intensity increases significantly with increasing cervical dilation.[21–23] We recruited both nulliparous and multiparous women, and also parturients receiving oxytocin augmentation. In contrast, Capogna *et al.*[17] recruited only nulliparous women and excluded parturients receiving oxytocin. Both primiparity and oxytocin augmentation of labor have been independently shown to be associated with greater pain during labor.[24–27]

The definition of effective analgesia has also differed among published studies and also contributes to differences in calculated drug potency or ED_{50} values. We defined an effective analgesic response as a reduction of VAS pain score during a contraction to 50% or less of baseline within 30 min after injection. This criterion has previously been described in studies of epidural bupivacaine.[28] In comparison, Polley *et al.*[10] and Capogna *et al.*[17] defined effective analgesia as a VAS pain score of 10 mm or less, whereas Beilin *et al.*[9] used the subjective assessment of the patient. Other definitions used for adequate analgesia that have been reported include the patient not requesting additional analgesia,[14] 90% or greater reduction in pain score,[16] and pain scores of no greater than 25[29] or 30 mm.[30]

In our study, we defined the time interval in which an analgesic response had to occur as 30 min, which is similar to the criteria adopted by other investigators studying the response to epidural as well as intrathecal drug administration.[10,13,14,17] We found that larger doses did not produce more rapid onset of analgesia. This is in contrast to studies of epidural bupivacaine in which larger doses of bupivacaine produced shorter onset times.[19,20] The onset time was 15–17.5 min in our patients, which is consistent with that reported by Eddleston *et al.*[1] and McCrae *et al.*[3]

We defined duration of analgesia as the time from drug injection until return of the pain score to 50% of baseline. Because duration of analgesia has been defined in different ways, we also recorded the time from injection to the patients' next request for analgesia and found these values were similar (table 3), suggesting that our

Table 3. Characteristics of Epidural Analgesia Attained

Group	20 mg (n = 15)	30 mg (n = 15)	40 mg (n = 15)	50 mg (n = 15)	*P* Value
Onset (min)*	17.5 (10.0, 25.0)	15.0 (11.3, 25.0)	15.0 (11.3, 23.8)	15.0 (10.0, 21.3)	0.93
Duration of analgesia† (min)*	85 (60, 130)	120 (80, 130)	90 (73, 140)	135 (108, 160)	0.12
Duration to "top-up" request‡ (min)*	105 (80, 138)	120 (110, 140)	90 (73, 150)	135 (108, 160)	0.21
Upper sensory level (dermatome)§	T9 (L1–T6)	T7 (L4–T2)	T6 (T12–T2)	T6 (T11–T2)	< 0.01
Time for two-segment regression (min)*	52.5 (35.0, 73.8)	55.0 (20.0, 72.5)	40.0 (30.0, 50.0)	25.0 (12.5, 73.8)	0.55
Motor block (Bromage scale > 0; n)	0	2	3	2	0.39

* Median (interquartile range). † Until return of pain score to 50% of baseline value. ‡ Until patient's first request for subsequent analgesia. § Median (range).

definition was clinically appropriate. The median duration of analgesia for the doses we studied (20–50 mg) ranged from 85 to 135 min, which is comparable with the results of Beilin *et al.*[9] (64–110 min with a dose range of 13–26 mg) and Polley *et al.*[10] (93.7 ± 28.6 min with doses of 20–24.4 mg). However, other studies have reported shorter durations of 62 min with 25–37.5 mg[1] and 52 min with 50 mg.[3]

We found the overall incidence of side effects was small and was not related to the dose of ropivacaine. In particular, we found a small incidence of motor block, which ranged from 13 to 20%. This is consistent with the findings of Muir *et al.*,[4] who reported a 21% incidence of motor block using 10 ml of 0.25% ropivacaine (25 mg). Conversely, greater incidences of motor block have been reported by Eddleston *et al.*[1] (25–37.5 mg) and McCrae *et al.*[3] (50 mg), with figures as great as 65%. Our incidence of hypotension was not significantly dose-related ($P = 0.61$) and was low (7–20%) compared with that of McCrae *et al.*[3] (30%).

Our study has several limitations. We did not discriminate parity or oxytocin use in our recruitment, which are potential confounding variables that may affect the severity of labor pain.[24–27] However, parity and oxytocin administration were evenly distributed among our groups. Our definition of an effective analgesic response was not as stringent as those used by some of the other investigators referred to in our discussion. However, we have confirmed *post priori* that our subjects spontaneously requested additional analgesia when pain score returned to 50% of their respective baseline, which suggests that our threshold of 50% of baseline was appropriate. Our sigmoid dose–response curve had a steep slope between 10 and 20 mg, with corresponding success rates of 0 and 66.7%. Inclusion of doses between 10 and 20 mg may have produced a "smoother" curve; however, the probit transformation produced a good fit linear regression with an r value of 0.84 ($r^2 = 0.71$). Finally, the CIs for our estimation of ED_{50} and ED_{95} were wide; this may have been improved if we had used a larger sample size or recruited a more homogenous study population by enrolling only nulliparous subjects, or excluded parturients receiving oxytocin augmentation.

In conclusion, we have determined a dose–response relation for single-dose epidural ropivacaine to establish analgesia in early labor and found the ED_{50} of ropivacaine to be 18.4 mg (95% CI, 13.4–25.4 mg).

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References

1. Eddleston JM, Holland JJ, Griffin RP, Corbett A, Horsman EL, Reynolds F: A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour. Br J Anaesth 1996; 76:66–71

2. Writer WDR, Stienstra R, Eddleston JM, Gatt SP, Griffin R, Gutsche BB, Joyce TH, Hedlund C, Heeroma K, Selander D: Neonatal outcome and mode of delivery after epidural analgesia for labour with ropivacaine and bupivacaine: A prospective meta-analysis. Br J Anaesth 1998; 81:713–7

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

4. Muir HA, Writer D, Douglas J, Weeks S, Gambling D, Macarthur A: Double-blind comparison of epidural ropivacaine 0.25% and bupivacaine 0.25%, for the relief of childbirth pain. Can J Anaesth 1997; 44:599–604

5. Stienstra R, Jonker TA, Bourdrez P, 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

6. Irestedt L, Ekblom A, Olofsson C, Dahlstrom AC, Emanuelsson BM: Pharmacokinetics and clinical effect during continuous epidural infusion with ropivacaine 2.5 mg/ml or bupivacaine 2.5 mg/ml for labour pain relief. Acta Anaesthesiol Scand 1998; 42:890–6

7. Gaiser RR, Venkateswaren P, Cheek TG, Persiley E, Buxbaum J, Hedge J, Joyce TH, Gutsche BB: Comparison of 0.25% ropivacaine and bupivacaine for epidural analgesia for labor and vaginal delivery. J Clin Anesth 1997; 9:564–8

8. Palmer CM, Cork RC, Hays R, Van Maren G, Alves D: The dose-response relation of intrathecal fentanyl for labor analgesia. ANESTHESIOLOGY 1998; 88: 355–61

9. Beilin Y, Galea M, Zahn J, Bodian CA: Epidural ropivacaine for the initiation of labor epidural analgesia: A dose finding study. Anesth Analg 1999; 88:1340–5

10. 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

11. Finney DJ: Probit Analysis. Cambridge, Cambridge University Press, 1971, pp 20–80

12. Lindstrom ML, Bates DM: Nonlinear mixed effects models for repeated measures data. Biometrics 1990; 46:673–87

13. Herman NL, Calicott R, Van Decar TK, Conlin G, Tilton J: Determination of the dose-response relationship for intrathecal sufentanil in laboring patients. Anesth Analg 1997; 84:1256–61

14. Arkoosh VA, Cooper M, Norris MC, Boxer L, Ferouz F, Silverman NS, Huffnagle HJ, Huffnagle S, Leighton BL: Intrathecal sufentanil dose response in nulliparous patients. ANESTHESIOLOGY 1998; 89:364–70

15. Lu JK, Schafer PG, Gardner TL, Pace NL, Zhang J, Niu S, Stanley TH, Bailey PL: The dose-response pharmacology of intrathecal sufentanil in female volunteers. Anesth Analg 1997; 85:372–9

16. Camann W, Abouleish A, Eisenach J, Hood D, Datta S: Intrathecal sufentanil and epidural bupivacaine for labor analgesia: Dose-response of individual agents and in combination. Reg Anesth Pain Med 1998; 23:457–62

17. Capogna G, Celleno D, Fusco P, Lyons G, and Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. Br J Anaesth 1999; 82:371–3

18. Dixon WJ, Massey FJ: Introduction to Statistical Analysis. New York, McGraw-Hill, 1983

19. Handley G, Perkins G: The addition of pethidine to epidural bupivacaine in labour: Effect of changing bupivacaine strength. Anaesth Intensive Care 1992; 20:151–5

20. Duggan J, Bowler GM, McClure JH, Wildsmith JA: Extradural block with bupivacaine: Influence of dose, volume, concentration and patient characteristics. Br J Anaesth 1988; 61:324–31

21. Brown ST, Campbell D, Kurtz A: Characteristics of labor pain at two stages of cervical dilation. Pain 1989; 38:289–95

22. Melzack R, Kinch R, Dobkin P, Lebrun M, Taenzer P: Severity of labour pain: Influence of physical as well as psychologic variables. Can Med Assoc J 1984; 130:579–84

23. Capogna G, Celleno D, Lyons G, Columb M, Fusco P: Minimum local analgesic concentration of extradural bupivacaine increases with progression of labour. Br J Anaesth 1998; 80:11–3

24. Sheiner E, Sheiner EK, Shoham-Vardi I: The relationship between parity and labor pain. Int J Gynaecol Obstet 1998; 63:287–8

25. Gaston-Johansson F, Fridh G, Turner-Norvell K: Progression of labor pain in primiparas and multiparas. Nurs Res 1988; 37:86–90

26. Cammu H, Verlaenen H, Amy JJ, De Koster K, Derde MP, Buekens P: Epidural analgesia in active management of labor. Acta Obstet Gynecol Scand 1994; 73:235–9

27. Corli O, Grossi E, Roma G, Battagliarin G: Correlation between subjective labour pain and uterine contractions: A clinical study. Pain 1986; 26:53–60

28. Christiaens F, Verborgh C, Dierick A, Camu F: Effects of diluent volume of a single dose of epidural bupivacaine in parturients during the first stage of labor. Reg Anesth Pain Med 1998; 23:134–41

29. Herman NL, Sheu KL, Van Decar TK, Rubin JD, Gadalla F, Koff HD, Reynolds JE: Determination of the analgesic dose-response relationship for epidural fentanyl and sufentanil with bupivacaine 0.125% in laboring patients. J Clin Anesth 1998; 10:670–7

30. Brownridge P: Epidural analgesia in the first stage of labour. Curr Anaesth Crit Care 1991; 2:92–100

Appendix 1

Equation for a standard Hill plot sigmoid curve (equation 1):

$$y = \frac{ax^b}{c^b + x^b}$$

Equation for a standard E_{max} sigmoidal curve (equation 2):

$$E = \frac{E_{max} \cdot Dose^{\partial}}{ED_{50}^{\partial} + Dose^{\partial}}$$

Substituting for these values from our results into equation 2 gives the equation:

$$Response = \frac{100 \times Dose^{2.8}}{18.8^{2.8} + Dose^{2.8}}$$