

ORIGINAL ARTICLE

Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour

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Background: The aim was to assess the effect of epidural sufentanil on relative analgesic potencies of epidural bupivacaine, ropivacaine and levobupivacaine by determining the minimum local analgesic concentrations during labour.

Methods: In a randomised, double-blind study, 171 parturients were allocated to one of six groups receiving a 10-mL bolus of bupivacaine, ropivacaine or levobupivacaine alone or with sufentanil 0.75 µg/mL. The concentration of local anaesthetic was determined by the response of the previous parturient using up-down sequential allocation starting at a concentration of 0.13% wt/vol with a testing interval of 0.01%. Effective analgesia was defined as a visual analogue pain score ≤15/100 mm within 30 min and lasting for 30 min. Median effective concentrations were estimated and two-sided $P < 0.05$ was significant.

Results: Local anaesthetic concentration, use of sufentanil and local anaesthetic drug were independent significant predictors of effective and ineffective analgesia. Bupivacaine was significantly more potent than levobupivacaine and ropivacaine. The relative potency ratios without sufentanil of 0.77:0.83:1.00 were reduced to 0.36:0.38:1.00 by the addition of sufentanil. The major factor influencing local anaesthetic requirements was the addition of sufentanil, which reduced overall requirements by a factor of 4.2 (95% CI 3.6–4.8); this effect was proportionately more enhanced for bupivacaine.

Conclusions: Local anaesthetic requirements for bupivacaine, levobupivacaine and ropivacaine follow an analgesic potency hierarchy. Any potency differences are small when compared to the effect of sufentanil, which resulted in a four-fold reduction in local anaesthetic requirements. Sufentanil may also enhance the potency differences between bupivacaine and the two S-enantiomer agents.

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INTRODUCTION

Epidural bupivacaine provides excellent pain relief during labour and delivery and is still the most widely used local anaesthetic in obstetric anaesthesia and analgesia. However, its use has disadvantages. Its potential for motor blockade and the risk of cardiovascular toxicity by accidental intravenous injection of high doses, initiated the search for other and safer local anaesthetics.^{1,2} Ropivacaine, an amino amide local anaesthetic that is structurally similar to bupivacaine, and levobupivacaine, the S-enantiomer of bupivacaine, have been investigated as possible alternatives.

Studies performed in animals and human volunteers have shown that both S-enantiomers, ropivacaine and levobupivacaine, are associated with less central

nervous system and cardiac toxicity than bupivacaine.²⁻⁴ Several studies in labouring parturients have also demonstrated that ropivacaine produces less motor block than bupivacaine.⁵⁻⁷ These differences were attributed to the chemical characteristics of ropivacaine, rather than to differences in potency. However, Polley et al. and Capogna et al. showed that ropivacaine was less potent than bupivacaine at the median effective concentration (EC50) point of the dose-response curve.^{8,9} Using the minimum local analgesic concentration (MLAC) methodology, these authors determined the EC50 for both ropivacaine and bupivacaine and observed a 40% difference in potency.^{8,9} This implied that both local anaesthetics could have similar toxic effects and motor blocking properties at equipotent concentrations.

Clinical evidence demonstrates that levobupivacaine has a similar potency to racemic bupivacaine.¹⁰⁻¹² Lyons et al. found levobupivacaine to be 13% less potent than bupivacaine using the MLAC methodology,¹⁰ while recently Polley et al. showed that levobupivacaine has a similar potency to ropivacaine.¹³

In modern obstetric analgesia, epidural opioids (sufentanil/fentanyl) are used to increase the potency of local anaesthetics.¹⁴ Opioids modify the MLAC of epidurally administered local anaesthetics in a dose-dependent way.¹⁵⁻²⁰ The effect of sufentanil on the relative potencies of bupivacaine, ropivacaine and levobupivacaine has not yet been investigated. It is unclear whether sufentanil can influence the relative potency of these agents. This is of clinical interest as most anaesthesiologists usually provide labour analgesia using combinations of opioids and local anaesthetics.

The aim of the present study was to evaluate the effect of epidural sufentanil on the relative analgesic potencies of bupivacaine, ropivacaine and levobupivacaine by determining the MLAC for these local anaesthetic agents.

MATERIALS AND METHODS

Following institutional ethics committee approval and written informed consent, 171 primiparous patients of ASA physical status 1 and 2 requesting epidural analgesia were enrolled in the study at the Heilig Hart Hospital, Roeselare, Belgium in a randomised, double-blinded sequential allocation study. All nulliparous women in active labour with cervical dilation of 2-6 cm and a visual analogue pain score (VAPS) of >30 mm (maximum 100 mm) requesting epidural analgesia were asked to participate. Participants had singleton pregnancies of more than 36 weeks' gestation with vertex fetal presentation without contraindications to epidural analgesia. Patients who received opioids or sedatives within 6 h before neuraxial analgesia were excluded.

After intravenous pre-hydration with lactated Ringer's solution (15-30 mL/kg), patients were placed in the flexed sitting position. After raising a midline skin wheal with 1% lidocaine, the epidural space was identified using loss of resistance to saline with an 18-gauge Tuohy needle at the L2-3 or L3-4 level, and a multiport epidural catheter (Perifix 20G, Braun, Melsungen) was advanced 3 to 5 cm in the epidural space. No test dose was used. Participants were allocated to one of six groups in a double-blinded, randomised, prospective study design to receive an epidural 10-mL bolus, given over 1 min; the first group (B) received bupivacaine (Marcaine®, AstraZeneca), the second group (BS) received bupivacaine with sufentanil 0.75 µg/mL (Sufentanil, Janssen Pharmaceutics), the third group (R) received ropivacaine (Naropin®, AstraZeneca), the fourth group (RS) received ropivacaine with sufentanil 0.75 µg/mL, the fifth group (L) received levobupivacaine (Chirocaine®, AstraZeneca) and the sixth group (LS) received levobupivacaine with sufentanil 0.75 µg/mL.

The concentration of local anaesthetic for the first parturient in each group was 0.13% wt/vol. The concentration of local anaesthetic received by each subsequent parturient was determined by the response of the previous parturient in that group to a higher or lower concentration, using an up-down sequential allocation technique as described by Dixon and Massey.²¹⁻²³ The testing interval was 0.01% wt/vol. Following insertion of the epidural catheter, patients were placed in the supine position with left uterine displacement. Blood pressure, pulse oximetry and tococardiography were monitored. Measurements were recorded at 5-min intervals.

Efficacy of the study drug was assessed using a 100 mm VAPS, where 0 represented 'no pain' and 100 'the worst possible pain' at 5-min intervals. VAPS was assessed during contraction, using a plastic ruler with the patient's side unmarked and the observer's side marked from 0 to 100 mm. A VAPS of ≤15 mm was defined as effective. Three outcomes were possible:

1. Effective: VAPS of ≤15 mm within 30 min of injection and lasting for 30 min after a VAPS ≤15/100 mm was reached. A result defined as effective directed a 0.01% decrement for the next patient randomised to that group.
2. Ineffective: VAPS >15 mm after 30 min or VAPS <15 mm within 15 min but not lasting for 30 min after a VAPS ≤15/100 mm was reached, but responding to rescue with a 10-mL bolus of 0.16% ropivacaine with sufentanil 1 µg/mL. A result defined as ineffective directed a 0.01% increment for the next patient in that group.
3. Reject: Patients not responding with a VAPS <15 mm within 30 min after the rescue bolus, indicating a failed epidural catheter due to pain not responsive

to rescue or indicating failure of spread (failing epidural). Parturients who stopped having contractions, who progressed beyond 7 cm cervical dilation or in which the fetal head descended below the ischial spines were also rejected. A result defined as a reject directed that the same concentration be repeated for the next patient randomised to that group.

At 30 min parturients not having effective analgesia were given the rescue bolus. Those not responding to rescue were designated as rejects and a new epidural catheter was placed. In addition to VAPS assessment, other data collected at 5-min intervals included maternal blood pressure, heart rate, oxygen saturation, uterine contractions, fetal heart rate, sensory level and motor block. Sensory level was determined by a perceived temperature difference to an ether swab. Motor block was assessed bilaterally at 15-min intervals using the modified Bromage scale of 0 = no motor block, 1 = inability to raise the extended leg, but able to move knees and feet, 2 = inability to raise the extended leg and to move knees, but able to move feet, and 3 = complete motor block of the lower limbs. To further assess motor block, patients with effective analgesia at 30 min were asked to keep both legs up for 30 s alternatively in a supine position. If patients were able to keep both legs up they were classified as having no motor block. For all women age, weight, height, gestation, cervical dilation, use of oxytocin infusion and presence of adverse effects, such as pruritus, nausea and vomiting, were recorded. Fetal data, such as birth weight, mode of delivery and Apgar scores were also recorded. At the end of the study period, analgesia was maintained using patient-controlled epidural analgesia (PCEA) with ropivacaine 0.17% and sufentanil 0.6 µg/mL with the possibility of a 2-mL bolus every 15 min. Patients could withdraw from the study at any time.

Statistical analysis

Demographic and obstetric data were collected and are presented as mean ± SD and count as appropriate.

Means ± SD were analysed using one-way and two-way analysis of variance (ANOVA) and counts or proportions were analysed using χ^2 tests. Median effective concentrations were estimated from the data using probit regression. The first run of patients, following the starting concentration, reacting identical to analgesia was not used. Only those who came after the first turn in the sequence in each group were used. To further minimise the bias of starting point and any failure of stabilisation, up-down estimates were also derived from the terminal six runs of patients in each group using the up-down method of Dixon and Massey, which enabled MLAC with 95% confidence intervals (CI) to be derived.^{22,23} Logistic regression was used to identify significant factors influencing effective or ineffective analgesia. Analyses were performed using the following software: Microsoft Excel 2000 (Redmond, WA), Number Cruncher Statistical Systems (NCSS 2004, Kaysville, UT) and Minitab 14 (State College, PA). Statistical significance was defined for an overall α error at the 0.05 level. All *P* values were two-sided.

RESULTS

The groups were similar with respect to pre-test variables such as demographic, obstetric and baseline VAPS data (Table 1). There were no significant differences in maternal or fetal haemodynamics and neonatal outcome data (Table 2). Eleven patients were rejected. Three patients were rejected because the epidural catheter failed (two in the BS-group and one in the R-group). Six patients entered the second stage of labour before the study was completed (two in the B-group, three in the R-group and one in the L-group). One patient in the L-group was rejected because labour stopped. Finally one patient in the RS-group was rejected because of protocol violation.

The up-down sequences are illustrated in Figs. 1 and 2. The MLAC (95% CI) results for each of the groups are listed in Table 3. Probit regression showed both groups (*P* = 0.021) and local anaesthetic concentration (*P* = 0.005) as significant factors with all groups being

Table 1. Demographic and obstetric data

	B (n = 24)	R (n = 24)	L (n = 25)	BS (n = 32)	RS (n = 28)	LS (n = 27)
Age (years)	27.1 ± 3.2	27.3 ± 4.9	26.8 ± 3.1	26.9 ± 3.8	26.4 ± 4.5	27.7 ± 3.1
Weight (kg)	80 ± 13	77 ± 12	76 ± 15	75 ± 14	77 ± 10	77 ± 15
Height (cm)	169 ± 5	166 ± 6	165 ± 7	161 ± 9	165 ± 7	164 ± 9
Gestation (wk)	39.7 ± 1.3	39.3 ± 1.1	39.5 ± 0.8	39.5 ± 1.0	40.0 ± 1.0	39.9 ± 1.1
Induced labour (%)	58	46	44	41	50	52
Cervical dilation (cm)	3.0 ± 1.3	2.8 ± 1.2	3.4 ± 1.1	3.1 ± 0.9	3.2 ± 1.1	2.9 ± 1.4
Cervical dilation at 60 min (cm)	3.8 ± 1.4	3.8 ± 1.9	3.8 ± 1.5	3.8 ± 1.4	3.7 ± 1.2	3.7 ± 1.7
Baseline VAPS	74 ± 13	70 ± 17	75 ± 21	66 ± 17	71 ± 20	73 ± 21

No statistically significant differences were identified. B: bupivacaine; R: ropivacaine; L: levobupivacaine; BS: bupivacaine-sufentanil; RS: ropivacaine-sufentanil; LS: levobupivacaine-sufentanil. VAPS: Visual Analogue Pain Scale. Data are mean ± SD or percent.

Table 2. Neonatal outcome data

	B (N = 24)	R (N = 24)	L (N = 25)	BS (N = 32)	RS (N = 28)	LS (N = 27)
Spontaneous delivery (%)	88	92	84	97	100	78
Apgar score <7 (%)	3	4	3	3	3	5
Weight (g)	3280 ± 392	3234 ± 431	3414 ± 444	3382 ± 410	3663 ± 360	3254 ± 499

No statistically significant differences were identified. B: bupivacaine; R: ropivacaine; L: levobupivacaine; BS: bupivacaine-sufentanil; RS: ropivacaine-sufentanil; LS: levobupivacaine-sufentanil.

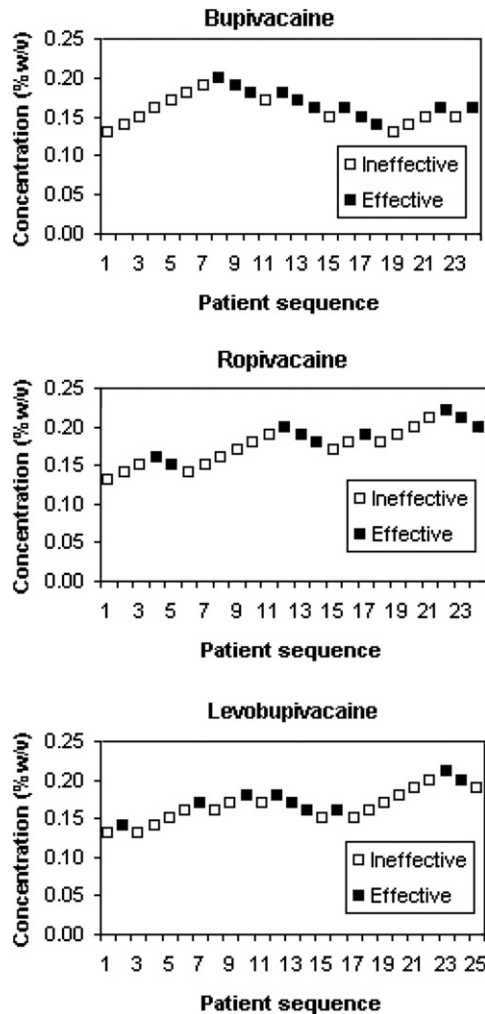


Fig. 1 The median effective local analgesic concentration of bupivacaine, ropivacaine and levobupivacaine as determined by the technique of up-and-down sequential allocation in patients in labour. The testing interval is 0.01% wt/vol. For minimum local analgesic concentrations see Table 3.

significantly different from bupivacaine ($P \leq 0.04$). Logistic regression confirmed local anaesthetic concentration ($P = 0.0024$), addition of sufentanil ($P = 0.00034$) and local anaesthetic ($P = 0.036$) as independent significant factors. The concentration of bupivacaine to achieve effective analgesia was significantly lower than that of both levobupivacaine ($P = 0.037$) and ropivacaine ($P = 0.024$). Two-way ANOVA also showed sig-

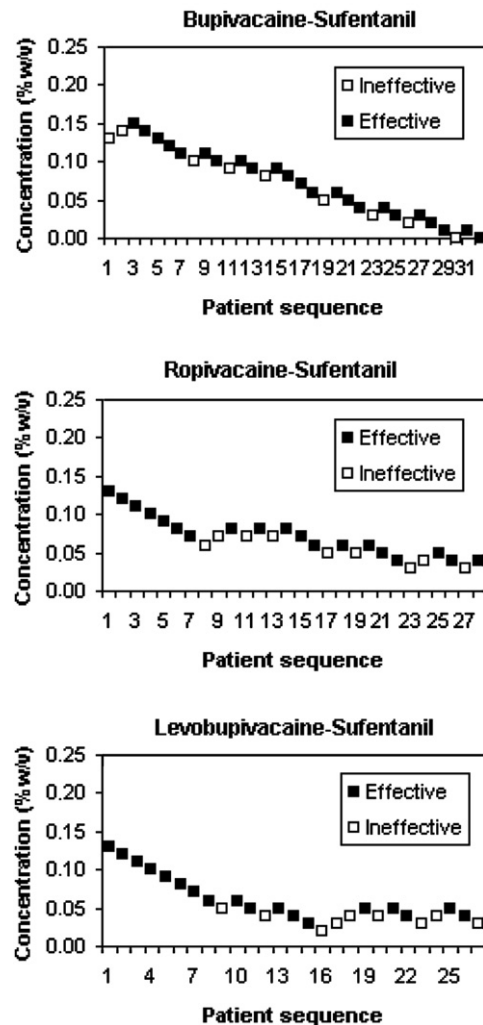


Fig. 2 The median effective local analgesic concentration of bupivacaine, ropivacaine and levobupivacaine, all with sufentanil 0.75 µg/mL, as determined by the technique of up-and-down sequential allocation in patients in labour. The testing interval is 0.01% wt/vol. For minimum local analgesic concentrations see Table 3.

nificant effects for both local anaesthetics ($P = 0.034$) and addition of sufentanil ($P < 0.0001$). The relative analgesic potency ratios of ropivacaine: levobupivacaine: bupivacaine alone of 0.77:0.83:1.00 respectively were reduced to 0.36:0.38:1.00 by the addition of sufentanil. The major factor therefore influencing local anaesthetic requirements was the addition of sufentanil, which

Table 3. Minimum local analgesic concentrations with 95% confidence intervals

Group	MLAC by Dixon & Massey ^a	Probit regression ^c	Probit <i>P</i>
Bupivacaine	0.149 (0.134-0.164)	0.139 (0.100-0.179)	Reference
Levobupivacaine	0.179 (0.138-0.220)	0.193 (0.156-0.228)	0.04
Ropivacaine	0.194 (0.170-0.217)	0.197 (0.162-0.232)	0.04
Bupivacaine-sufentanil	0.015 (0.000-0.041) ^b	0.012 (0.000-0.052)	0.008
Levobupivacaine-sufentanil	0.040 (0.030-0.050) ^b	0.032 (0.000-0.067)	0.027
Ropivacaine-sufentanil	0.042 (0.030-0.053) ^b	0.018 (0.006-0.075)	0.029

MLAC by Dixon and Massey: Minimum local analgesic concentration with 95% confidence intervals as determined by the method described by Dixon and Massey.

^aTwo-way ANOVA; *P* = 0.034 for effect of local anaesthetic, *P* < 0.0001 for effect of sufentanil.

^bBonferroni post-tests *P* < 0.001 for sufentanil groups versus local anaesthetic alone.

^cProbit *P* values; *P* = 0.021 for effect of local anaesthetic, *P* = 0.005 for effect of sufentanil.

reduced overall requirements by a factor of 4.2 (95% CI 3.6-4.8) and this effect was proportionately more enhanced for bupivacaine. Bupivacaine requirements were reduced by a factor of 9.9 (95% CI 2.8-35.1) with the addition of sufentanil, whilst the ropivacaine and levobupivacaine requirements were only reduced by a factor of 4.6 (95% CI 2.4-14.8) and 4.5 (95% CI 2.3-14.6) respectively as a result of the addition of sufentanil.

There were no significant differences between the groups in sensory block. No patient developed motor block as determined by the modified Bromage score. There were no significant differences in the groups in the incidence of pruritus, nausea or vomiting and no treatment was required.

DISCUSSION

Direct comparison between bupivacaine, ropivacaine and levobupivacaine without the addition of epidural sufentanil

This study is, to our knowledge, the first to compare bupivacaine, ropivacaine and levobupivacaine and the effect of sufentanil simultaneously using the MLAC methodology. Two previous studies have directly compared ropivacaine and bupivacaine^{8,9} whilst another has investigated the relative potencies of bupivacaine and levobupivacaine.¹⁰ Polley et al.⁸ and Capogna et al.⁹ found a potency ratio of 0.60, implying that ropivacaine was 40% less potent than bupivacaine. Lyons et al.¹⁰ found levobupivacaine to be slightly less potent than bupivacaine. As a result of these three studies it was generally assumed that levobupivacaine and bupivacaine are of similar potency, whilst ropivacaine is significantly less potent. Two further studies provided some confusion as to the respective position of levobupivacaine.^{13,24} The latter studies suggested that levobupivacaine was of similar potency to ropivacaine.^{13,24} Data from epidural motor block and intrathecal analgesia studies have emerged with a clear and more consistent potency hierarchy: bupivacaine >

levobupivacaine > ropivacaine.²⁵⁻²⁷ The present study is consistent with these findings.

We also found higher MLAC values for all three local anaesthetics than those previously reported. Changes in methodology may account for these differences. This study used a 10-mL rather than the 20-mL bolus used in previous work. The lesser volumes can be expected to result in compensatory increases in concentration or dose requirement. The actual doses of local anaesthetic, corresponding to the calculated MLAC values in the present study, are however similar to those previously reported.⁸⁻¹⁰ Also our protocol allowed for an increase in oxytocin infusion during the study period, which may have contributed to greater analgesic requirements. Furthermore, it is always difficult to compare MLAC values from centre to centre as patient characteristics, anaesthetic practice, labour characteristics and obstetric practice may vary.

The effect of adding epidural sufentanil on the relative potencies of ropivacaine, bupivacaine and levobupivacaine

The MLAC model in epidural analgesia not only provides an estimate of the analgesic potency of a local anaesthetic, but also allows the effect of adding opioids on the potency of those local anaesthetics to be quantified. Previous studies have shown the local anaesthetic sparing ability of sufentanil, using epidural infusions of local anaesthetic with varying opioid concentrations, repeated epidural injections, or both.²⁸⁻³¹ There are only a few recent studies using the MLAC model.

We studied the effect of sufentanil 0.75 µg/mL on the MLAC of bupivacaine, ropivacaine and levobupivacaine. The MLAC of bupivacaine decreased 90% when sufentanil was added. Polley et al.¹⁸ described significant dose-dependent reductions of the MLAC of bupivacaine by sufentanil, using three different sufentanil doses (0.5, 1.0, 1.5 µg/mL); our reduction is at least consistent with, if not greater than, those data. We found that the MLAC of ropivacaine and levobupivacaine decreased by approximately 78%. This effect exceeded

that found by Palm et al.¹⁷ who reported only a 31% reduction in MLAC of ropivacaine when sufentanil 0.75 µg/mL was added. Robinson et al.¹⁴ reported a 50% reduction when fentanyl 2-3 µg/mL was added to levobupivacaine. The present trial therefore indicates that adding sufentanil to the epidural analgesic mixture significantly increases the potency of all three local anaesthetic agents and to a larger extent than previously reported. Differences in MLAC methodology, in patient populations and obstetric practices may account for the observed variations.

It is interesting to consider the effect of sufentanil on the relative analgesic potency ratios of the three pipecoloxylidines. Our data, and indeed the previous studies, suggest that the effect of an opioid is proportionately greater for racemic bupivacaine than for ropivacaine and levobupivacaine. As Palm et al.¹⁷ postulated, one might assume that the reduction of MLAC by addition of an opioid is more pronounced for local anaesthetics with higher analgesic potency, such as bupivacaine. This appears to be supported by our data. We found that the relative potency ratios without sufentanil of 0.77:0.83:1.00 were reduced to 0.36:0.38:1.00 by the addition of sufentanil. So, sufentanil might not only enhance the potency of the local anaesthetics by reducing MLAC, it might also increase the difference in potencies between the local anaesthetics. Whilst of course this is of some pharmacological interest, it is important to keep this in perspective. The absolute concentrations are sufficiently low that any differences are unlikely to be of real clinical importance.

MLAC methodology

The present trial differs in methodology from previous MLAC studies. First of all we wished to compare all three local anaesthetics in the same trial, patient population and obstetric practice. Moreover, to our knowledge we are also the first to evaluate the effect of adding epidural opioids on the relative potencies of different local anaesthetic agents. Secondly, two alterations have been made to the usual MLAC-methodology.²¹ Instead of using a 20-mL dose (to give each concentration being tested every possible chance to achieve adequate spread), we used a 10-mL dose. We also considered a VAPS of ≤15 mm within 30 min and lasting for 30 min, as effective, instead of a VAPS ≤10 mm within 30 min. The reason for the first alteration is of a practical and clinical nature. Our standard practice is to administer a 10-mL loading dose in the epidural space. This is also standard practice in most obstetric anaesthesia units throughout Belgium. As this practice works well, we wanted to test the MLAC methodology using a 10-mL bolus. We accepted that this change in methodology might have affected the MLAC estimates, but we

feel it is unlikely that it would affect the relative potencies of different local anaesthetic agents. To compensate for a possible lesser spread of local anaesthetic we allowed a VAPS of ≤15 mm, but we required a time interval of 30 min in which the VAPS had to stay less than 15 mm to avoid false positive results. Retrospective review of the data showed that most of the effective results were actually achieved with a VAPS <10 mm within 30 min and lasting for 30 min.

The starting concentration in some of the groups combining local anaesthetic with sufentanil is significantly different from the actual observed MLAC concentration. It would be ideal to start at a concentration close to the actual MLAC concentration to improve the validity of the study results. However, if we already knew the MLAC concentration before the start of the study, there would be no real reason to do the trial. As a result of the important difference between actual MLAC and starting concentration in the sufentanil groups, we probably underestimated the effect of sufentanil. This is an important issue that might have affected the potency ratios we reported, so caution should be exercised when interpreting our results.

CONCLUSION

Although previous studies have compared racemic bupivacaine, levobupivacaine and ropivacaine, the present trial is the first to compare all three within one study. Furthermore, the present trial is the first that evaluates the effects of sufentanil on MLAC of all three local anaesthetics in the same study. This study confirms the epidural analgesic potency hierarchy of ropivacaine, levobupivacaine and racemic bupivacaine with the racemate as the most potent. Addition of sufentanil reduces local anaesthetic requirements to a clinically important extent. The potency of bupivacaine is proportionately more enhanced by sufentanil but differences in absolute concentrations achieved are of pharmacological rather than clinical interest. Clinically, the effect of an opioid is more important than any differences relating to the relative potencies of the pipecoloxylidine local anaesthetics. It must also be stressed that this investigation is the first to use a 10-mL epidural bolus of local anaesthetic solution. Although this is uncommon methodology for MLAC studies, it is common anaesthetic practice in certain areas and the present results are therefore of value to the reader.

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