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RESEARCH PAPER

# Analgesic and motor-blocking action of epidurally administered levobupivacaine or bupivacaine in the conscious dog

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## Abstract

**Objective** To compare the analgesic and motor-blocking effects of epidurally administered levobupivacaine and bupivacaine in the conscious dog.

**Study design** Prospective, randomized, cross-over study.

**Animals** Six adult female Beagle dogs.

**Methods** Each animal received three doses of levobupivacaine or bupivacaine (0.5, 1.0 and 1.5 mg $kg^{-1}$; concentrations 0.25%, 0.50%, and 0.75%, respectively) in a total volume of 0.2 mL $kg^{-1}$ by means of a chronically implanted epidural catheter. Onset, duration (through pinch response in the sacral, lumbar and toe areas) and degree of analgesia and motor-blocking status was determined with a scoring system and at regular intervals over 8.5 hours before (baseline) and after drug administration.

**Results** Epidurally administered levobupivacaine and bupivacaine had a similar dose-dependent analgesic action with no significant differences in onset (range: 5–8 minutes), duration (bupivacaine: 42 ± 28, 135 ± 68 and 265 ± 68 minutes, and levobupivacaine: 28 ± 33, 79 ± 55 and 292 ± 133 minutes; 0.25%, 0.50%, and 0.75%, respectively) or maximum degree of analgesia. However, levobupivacaine tended to produce a shorter duration of motor block than bupivacaine and the difference in the motor to nociceptive blockade times was significant at the highest dose.

**Conclusion** Epidural levobupivacaine produced an analgesic action similar to that of bupivacaine.

**Clinical relevance** Epidural levobupivacaine is suitable for clinical use in dogs, mostly at the highest dose if a high degree of analgesia is required.

*Keywords* bupivacaine, dog, epidural anaesthesia, levobupivacaine, local anaesthetics.

## Introduction

Bupivacaine (BUP) is a local anaesthetic, employed in dogs, to produce long-lasting caudal analgesia when administered into the epidural space (Hendrix et al. 1996; Jones 2001). Chemically, BUP (1-butyl-N-(2,6-dimethylphenyl) piperidine-2-carboxamide) has a chiral centre and therefore exists as a 50:50 mixture of two enantiomers, levobupivacaine (S(-)-BUP; L-BUP) and dextrobupivacaine (R(+)-BUP) with similar potency and duration of action (Cox et al. 1998; Foster & Markham 2000; McLeod & Burke 2001). Although relatively safe, local anaesthetics are not devoid of toxicity and may induce

undesired cardiac and neurological effects; specifically, BUP has a relatively reduced margin of safety compared with other common local anaesthetics like lidocaine, particularly when accidentally administered via the intravascular route (Gristwood 2002). Experimental and human clinical studies have compared L-BUP with BUP and suggested that L-BUP is less cardiotoxic (Bardsley et al. 1998; Huang et al. 1998; Gristwood 2002). This stereoselective effect is likely to be due partly to the pharmacokinetic differences between the enantiomers, specifically regarding tissue retention and plasma protein binding (Burm et al. 1994). Nevertheless, the reduced cardiac toxicity of L-BUP is apparently not at the expense of its efficacy or potency (Cox et al. 1998; Kopacz et al. 2000), even though clinical observations in humans have suggested that L-BUP is a less potent analgesic than BUP (Camorcia et al. 2005).

The pharmacokinetic and motor block effects of L-BUP administered intravenously (IV; 1.0 mg $kg^{-1}$) and via the epidural route (1.8 mg $kg^{-1}$) have been studied in dogs (Franquelo et al. 1999), but further examination of different concentrations of L-BUP and the resulting analgesic actions using the epidural route has yet to be reported. The local anaesthetic L-BUP provides a more desirable clinical profile compared with BUP, characterized by a similar degree of sensory and motor blockade, but with lower toxicity (Foster & Markham 2000). However, the duration of analgesia with L-BUP in humans is longer than with racemic BUP whereas the duration of the motor block is similar with both drugs (Kopacz et al. 2000). The aim of this study was to compare the analgesic and motor blockade actions of L-BUP with those of BUP when administered into the epidural space of conscious dogs. The hypothesis was that the analgesic effect of L-BUP would not differ from that produced by BUP, although a lower degree of motor block could be expected when similar doses are given by the epidural route.

## Material and methods

The study was conducted after institutional approval for animal experimentation. Six adult female Beagle dogs weighing 14.2–17.7 kg (15.6 ± 1.2 kg; mean ± SD) and aged 20–24 months old (22 ± 1 months; mean ± SD) were used (Instituto de Salud Carlos III, Majadahonda, Spain). Each dog received BUP (0.25%, 0.50% and 0.75%; Inibsa, Barcelona, Spain) and L-BUP (0.25%, 0.50% and 0.75%; Abbott Laboratories, Madrid, Spain) at three doses (0.5, 1.0 and 1.5 mg $kg^{-1}$; concentrations 0.25%, 0.50% and 0.75%, respectively) for each drug in a randomized order.

### Epidural catheter placement procedure

One week before the first study each dog was anaesthetized with medetomidine [30 μg $kg^{-1}$ intramuscular (IM); Pfizer, Madrid, Spain] and isoflurane administered to effect through a facemask. The animal was monitored by means of ECG (lead II) and pulse oximetry.

Under sterile conditions, an 18-gauge Tuohy needle (Epidural anaesthesia set Perifix 421. B. Braun, Melsungen, Germany) was introduced into the lumbosacral space ($L_7$-$S_1$). The 'loss-of-resistance' technique was employed to identify the epidural space, which was considered the point at which there was negligible resistance to the injection of 1 mL of air. An epidural catheter was advanced through the needle to a total length from the insertion point of 6.5 cm in all animals; with the tip of the catheter located approximately 4 cm cranially to the lumbosacral space (cranial portion of $L_6$). The catheter was cut to a total length of 25 cm and connected to a valve (Intraven, Madrid, Spain), placed subcutaneously (SC), and the incision was closed. An antibiotic (Cephazoline, 30 mg $kg^{-1}$ IM; Normon, Madrid, Spain) was administered before the procedure and an alpha-2 adrenergic antagonist, atipamezole (0.25 mg $kg^{-1}$ IM; Pfizer, Madrid, Spain), was administered after the procedure. A test dose of 2 mL of lidocaine 1% (Inibsa, Madrid, Spain) was injected percutaneously through the valve to ensure proper positioning of the catheter, and this was confirmed by the observation of ataxia and reduced sensitivity to pinching the pelvic limbs.

### Local anaesthetic evaluation

Each animal received three doses of L-BUP or BUP in a blinded random fashion and the time between experiments in a single dog was at least 1 week. Experiments were scheduled twice a week. The drugs were injected slowly (45 seconds) through the skin into the SC valve. All animals received a fixed total volume of 0.2 mL $kg^{-1}$ at different doses/concentrations of the drug, followed by 0.3 mL saline solution to flush the dead space in the valve

  

and catheter. Analgesia and motor status were qualitatively assessed as described previously (Gomez de Segura et al. 2000) at regular intervals: baseline (2–5 minutes before drug administration, defined as minute 0 in Figs 1–3), 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 and then every 30 minutes thereafter until minute 510. Evaluation of the effects of the studied drugs was always performed by the same experimenter (AM) who was blinded to the drug and dose given.

### Analgesia

Nocifensive response blockade was assessed in three areas of the body (Kitchell & Evans 1993): Left hind toe web ($L_5$-$L_7$ dermatomes), sacral area ($L_2$-$L_5$ dermatomes) and caudodorsal area of the ribs (lumbar area; $T_{12}$-$L_1$ dermatomes). Toe web analgesia was assessed by applying a standard nociceptive stimulus to the left pelvic limb toenail base in all four weight-bearing toes, with a haemostatic forceps (8-inch Rochester Dean Haemostatic Forceps; Martin, Tuttlingen, Germany) clamped at the first ratchet lock. Two further regions, sacral and lumbar, were tested for analgesia to a bilateral skin pinch from an Allis forceps (Martin) and were recorded in a caudo-cranial direction. A positive response was considered as the reflex contraction of the skin (Feldman et al. 1996).

### Toenail base pinch response

A 3-point rating scale was used: 1) normal response: pelvic limb withdrawal and/or vocalization; 2) reduced response; and 3) no response.

### Skin pinch response

A 2-point rating scale was used for sacral and lumbar area dermatomes: 1 – normal response: muscle contraction; and 2 – no response. A third rating scale point was not included as it might be considered as difficult to distinguish from the two other rating scale points. The different study times (in minutes) were defined as follows: *Time to onset of analgesia:* time from drug administration to the appearance of some degree of analgesia (score >1). *Time to onset of complete analgesia*: time from drug administration to the appearance of complete analgesia (score = 3). *Duration of analgesia:* time during which analgesia, whether partial or complete, was observed (score >1). *Duration of complete analgesia:* time during which complete analgesia was observed (score = 3). *Duration of recovery from analgesia:* time elapsed from the last point at which the maximum degree of analgesia was observed until normal nocifensive response was regained. When considering skin pinch response, only complete analgesia could be assessed. Special attention was paid to ascertaining that the response of the animal to the stimulus (sudden withdrawal,

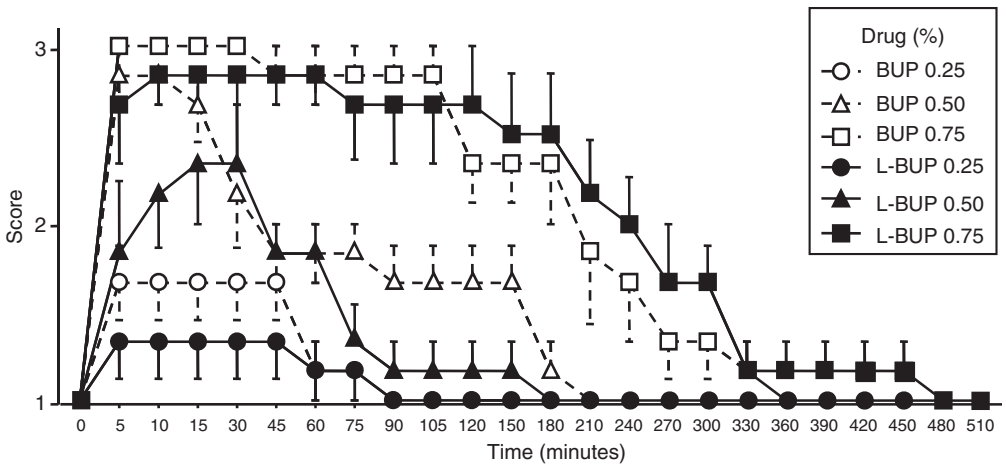


**Figure 1** Toenail base pinch response blockade. Time-course response to toenail base pinch of dogs given 0.2 mL $kg^{-1}$ of levobupivacaine (L-BUP) and bupivacaine (BUP) 0.25%, 0.50% and 0.75% in the epidural space. Toenail base pinch response score: 1 – normal response, 2 – reduced response, and 3 – no response. No significant differences were found when comparing the same concentrations of either drug. Data are expressed as mean ± SEM ($n$ = 6); SEM and not SD is used in figures for clarity.

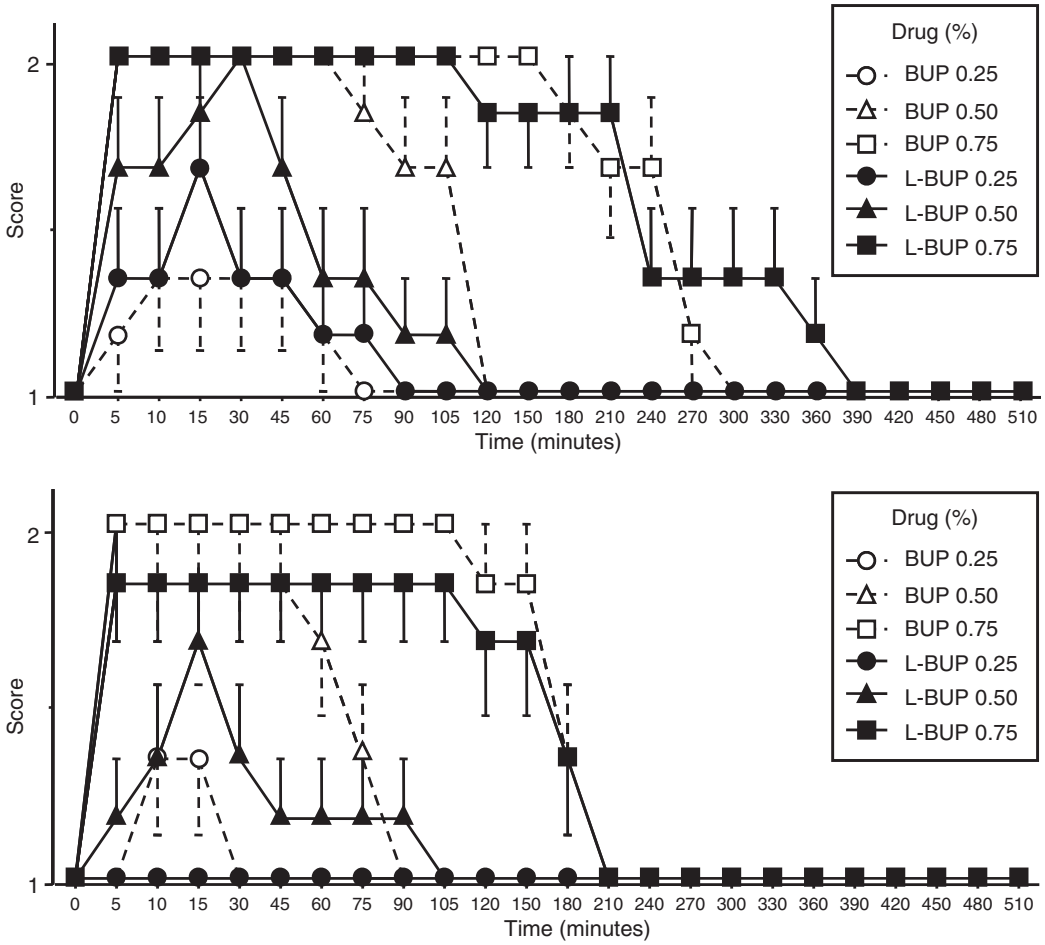


**Figure 2** Skin pinch response blockade in sacral area (top) and lumbar area (bottom) dermatomes. Time-course response to skin pinch of the sacral area of dogs indicated in Fig. 1. Skin pinch response score: 1 – normal response, 2 – no response. No significant differences were found when comparing the same concentrations of either drug. Data are expressed as mean ± SEM ($n$ = 6); SEM and not SD is used in figures for clarity.

head turn or vocalization), was not a consequence of a learned behaviour but a normal response to a painful stimulus (toenail base pinch or skin pinch). Therefore, non-noxious stimuli were applied when necessary, by touching the toenail base. This was performed when animals had sensitivity and presented a nocifensive response, before administering the drug or when the analgesic effect wore off. The possibility of learned behaviour was minimized by randomization or the experiments.

### Motor blockade

Motor blockade was assessed by observing the animal while walking or evaluating its ability to stand on its pelvic limbs. A 3-point rating scale was used: 1 – normal motor response: normal ability to walk or stand using the pelvic limbs; 2 – partial motor blockade: presence of ataxia; and 3 – complete motor blockade: inability to stand on the pelvic limbs, paralysis. The different study times (in minutes) were defined as follows: *Time to onset of complete motor blockade:* time from drug administration to the time at which complete motor blockade appeared (score = 3). *Duration of complete motor blockade:* time during which complete motor blockade was observed (score = 3). *Duration of motor blockade:* time during which partial or complete motor blockade was observed (score >1). *Duration of recovery of motor blockade*: time from the last point at which maximum degree of motor blockade was observed until normal motor response was regained

  

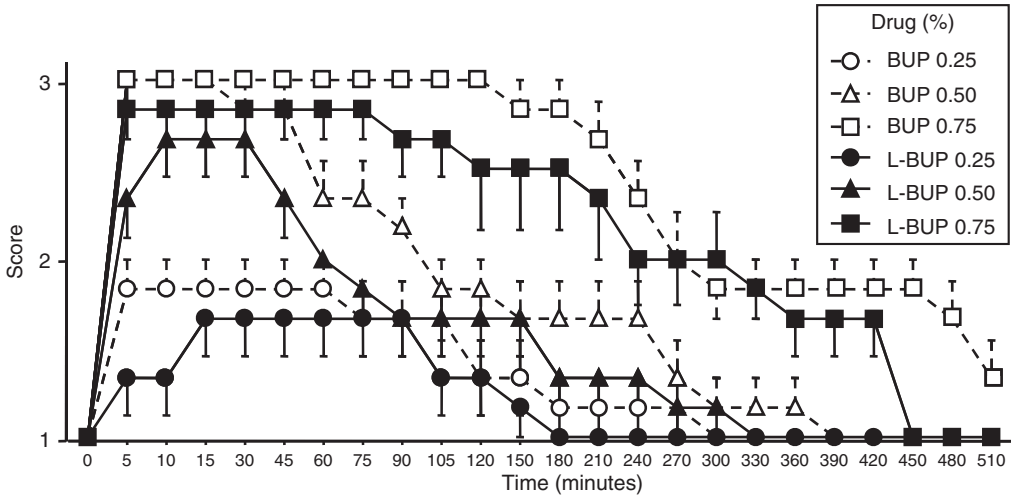


**Figure 3** *Motor blockade.* Time-course response of dogs as indicated in Fig. 1. Motor blockade score: 1 – normal motor response, 2 – partial motor block, and 3 – complete motor blockade. No significant differences were found when comparing the same concentrations of either drug. Data are expressed as mean ± SEM ($n$ = 6); SEM and not SD is used in figures for clarity.

without ataxia. Analgesia and motor-blocking status were assessed until normal function was regained. The last assessment was performed 30 minutes after the first normal response to the noxious stimulus and normal motor function was recorded.

### Motor blockade to analgesia time difference

The difference, in minutes, between the duration of the analgesic effect at the toes and the duration of motor blockade produced by the studied drugs and doses was calculated.

Data are expressed as mean ± SD. Nocifensive and motor responses plotted against time (in minutes) are provided as mean ± SEM for clarity in Figs. 1–3. The $n$ value was always six for every drug and dose with the exception of onset of analgesia, where those animals in which a nocifensive response was not observed were not included in the calculation of the mean value. An analysis of variance was performed to determine the influence of the drug (L-BUP or BUP) and dose (0.25%, 0.50%, 0.75%) variables, and whether the dose affected the analgesic and motor-blocking status and its duration in a dose-dependent fashion. However, different doses of the same drug were not compared. To compare equal doses, one-way ANOVA test and the ANOVA test for repeated measures was used ($n$ = 6). A value of $p < 0.05$ was considered statistically significant. The statistical package SPSS 15.0 (Cary, NC, USA) was used.

## Results

None of the animals was excluded from the study. It was necessary to re-implant a catheter in one dog after it was found to be dislodged when a test dose of lidocaine failed to produce the expected analgesic effect. A slight contraction of the lumbar area during the epidural administration of the drugs was observed in most cases. All animals recovered uneventfully and catheters were implanted for up to 18 weeks.

### Analgesia

#### *Toenail base pinch response blockade*

The mean onset to analgesia took 10 minutes or less in all groups (BUP at all doses: 5 minutes; L-BUP: 6–8 minutes), although the low dose of both drugs did not produce analgesia in all dogs (Fig. 1, Table 1). Toenail base pinch analgesia was dose-dependent for both BUP and L-BUP and no significant differences were found when the same dose/concentration of either drug was administered. Maximum blockade scores for 0.25%, 0.50%, and 0.75% BUP (1.8, 2.8, 3.0, respectively; range: 1–3) and L-BUP (1.7, 2.3, 2.8, respectively; range: 1–3) were also similar (Table 1). Also, the duration of

toenail base pinch analgesia was similar at equal doses (Table 1) of BUP (42, 135 and 265 minutes with 0.25%, 0.50%, and 0.75%, respectively) and L-BUP (28, 79 and 292 minutes with 0.25%, 0.50%, and 0.75%, respectively) in those animals where the effect was observed. There was a total lack of response to the noxious stimulus in all animals ($n = 6$) only at the highest concentration of BUP (0.75%; group score 3.0), whereas with L-BUP 0.75%, one of the six dogs did not have complete analgesia to toe pinch (group score 2.8). No dog had complete analgesia at the low concentration of either drug (0.25%).

*Skin pinch response blockade*

The degree of dermatome blockade decreased in a caudal-to-cranial fashion; sacral area dermatomes were more affected than lumbar area dermatomes (Fig. 2, Table 1). The degree of dermatome blockade and the duration was significantly dose-dependent for both BUP and L-BUP. The blockade was always equal or less potent in the lumbar area than the sacral area dermatomes. Maximum blockade scores in the studied dermatomes were for 0.25%, 0.50%, and 0.75%, respectively (range: 1–2): BUP, Sacral area: 1.3 ± 0.5, 2.0 ± 0.0, 2.0 ± 0.0; Lumbar area: 1.3 ± 0.5, 1.8 ± 0.4, 2.0 ± 0.0; L-BUP, Sacral area: 1.8 ± 0.4, 2.0 ± 0.0, 2.0 ± 0.0; Lumbar area: 1.0 ± 0.0, 1.7 ± 0.5, 1.8 ± 0.4. The scores were similar (nonsignificant differences) for the two drugs except with the middle dose, at which the analgesic effect of L-BUP was significantly less potent than that of BUP in the lumbar and sacral area dermatomes (Table 1). Complete analgesia was observed in sacral area dermatomes in all animals receiving the middle and high doses of each drug, whereas only animals receiving BUP 0.75% had a complete blockade in the lumbar dermatomes. Conversely, L-BUP 0.25% had no analgesic effects in the lumbar area dermatome in any dog.

Observed time to onset of lumbar area and sacral area dermatome blockade was within 5 minutes in all animals which received the two high doses of each drug or within 10 minutes in animals receiving the low dose of BUP. However, as indicated, the lumbar area dermatome was not blocked in dogs given L-BUP 0.25%. The maximum degree of dermatome block was always obtained within the first 30 minutes (score 2.0). Duration of skin pinch analgesia was dose-dependent ($p < 0.05$) and similar for BUP and L-BUP (Table 1, Fig. 2). The duration of the sacral area dermatome blockade produced by BUP (24, 100 and 235 minutes with 0.25%, 0.50%, and 0.75%, respectively) and L-BUP (30, 61 and 260 minutes with 0.25%, 0.50%, and

**Table 1** Toenail base pinch response blockade and skin-pinch response blockade of vertebral dermatomes receiving 0.2 mL $kg^{-1}$ of levobupivacaine (L-BUP) and bupivacaine (BUP) 0.25%, 0.50% and 0.75% in the epidural space

| | | Toenail base pinch response blockade | | | | Skin-pinch response blockade of vertebral dermatomes | |
|---|---|---|---|---|---|---|---|
| Drug | % | Maximum score (n = 6) (1–3)† | Onset of analgesia (score >1) (minutes)* | Duration of analgesia (score >1) (minutes)* | Duration of complete analgesia (score = 3) (minutes)* | Duration of sacral area analgesia (score = 2) (minutes)* | Duration of lumbar area analgesia (score = 2) (minutes)* |
| BUP | 0.25 | 1.8 ± 0.4 | 5 ± 0 (5) | 42 ± 28 (5) | 0 ± 0 (0) | 24 ± 30 (3) | 8 ± 10 |
| | 0.50 | 2.8 ± 0.4 | 5 ± 0 (6) | 135 ± 68 (6) | 23 ± 16 (5) | 100 ± 19 (6) | 53 ± 32 |
| | 0.75 | 3.0 ± 0.0 | 5 ± 0 (6) | 265 ± 68 (6) | 153 ± 84 (6) | 235 ± 38 (6) | 175 ± 33 |
| L-BUP | 0.25 | 1.7 ± 0.5 | 6 ± 3 (4) | 28 ± 33 (4) | 0 ± 0 (0) | 30 ± 31 (5) | 0 ± 0 |
| | 0.50 | 2.3 ± 0.5 | 8 ± 4 (6) | 79 ± 55 (6) | 16 ± 20 (2) | 61 ± 36 (6) | 27 ± 38 |
| | 0.75 | 2.8 ± 0.4 | 6 ± 2 (6) | 292 ± 133 (6) | 176 ± 100 (5) | 260 ± 110 (6) | 136 ± 73 |

Toenail base pinch response score: 1 – normal response, 2 – reduced response, and 3 – no response. Skin pinch response score: 1 – normal response, 2 – no response. Data are expressed as mean ± SD.

*Number of animals out of six contributing to the data set are given in parentheses; mean values are also calculated from this data set; †toenail base pinch response blockade 'Maximum score': no significant differences were found for the same concentration of BUP and L-BUP ($p < 0.05$; $n = 6$).

  

0.75%, respectively) was dose-dependent. The duration of lumbar area dermatome blockade produced by BUP (8, 53 and 175 minutes with 0.25%, 0.50%, and 0.75%, respectively) and L-BUP (0, 27 and 136 minutes with 0.25%, 0.50%, and 0.75%, respectively) was also dose-dependent and shorter than the duration of the sacral area blockade. Only when BUP 0.75% was administered, did all dogs present a blockade of the lumbar area dermatome, whereas at lower BUP doses or any of the three L-BUP doses studied, not all dogs were blocked at the lumbar area dermatome (Table 1). The duration of complete sacral area dermatome blockade achieved with the high dose of either drug was 100–145 minutes (from minute 5 to minute 150 with BUP and to minute 105 with L-BUP; Fig. 2, score 2) whereas BUP 0.50% (middle dose) produced only 55 minutes of complete blockade (from minute 5 to minute 60; Fig. 2, score 2). Recovery time in dermatomes was dose-dependent; it was the longest with the highest concentration (0.75%) and the shortest with the lowest concentration of each drug.

## Motor blockade

Motor blockade produced by BUP and L-BUP was dose-dependent ($p < 0.05$) and maximum blockade scores for 0.25%, 0.50%, and 0.75% were similar, 1.8, 3.0, 3.0 and 1.7, 2.7, 2.8, respectively (range: 1–3; Table 2, Fig. 3). Complete motor blockade was not observed in dogs which received the lowest doses/concentrations of both anaesthetics. When the middle and the highest doses/concentrations of the local analgesics were administered, only BUP produced complete motor blockade in all six dogs.

When ataxia was observed (see Duration of motor blockade, Table 2), onset time was between 5 minutes (BUP 0.25%, 0.50%, and 0.75% and L-BUP 0.50%, and 0.75%) and 7.5 minutes (L-BUP 0.25%). The duration of motor blockade produced by BUP (Motor blockade: 128, 238 and 493 minutes, Complete motor blockade: 0, 65 and 225 minutes with 0.25%, 0.50%, and 0.75%, respectively) and L-BUP (Motor blockade: 83, 183 and 360 minutes, Complete motor blockade: 0, 28 and 166 minutes with 0.25%, 0.50%, and 0.75%, respectively) were similar for a given concentration of either drug and were dose-dependent ($p < 0.05$). Duration of motor blockade, whether ataxia or paralysis of the pelvic limbs, was always, although not significantly, longer following BUP than following L-BUP at the same doses and concentrations. However, duration of recovery from motor blockade was similar with both drugs.

## Difference between motor blockade and analgesia duration

The duration of the motor blockade produced with either BUP or L-BUP was always more prolonged than that of analgesia (Difference: BUP 75, 103 and 228 minutes and L-BUP 55, 103 and 68 minutes, with 0.25%, 0.50%, and 0.75%, respectively. $n = 6$)

**Table 2** Motor blockade of animals receiving 0.2 mL kg$^{-1}$ of levobupivacaine (L-BUP) and bupivacaine (BUP) 0.25%, 0.50% and 0.75% in the epidural space

| Drug | % | Maximum score (1–3; $n = 6$)† | Duration of motor blockade (score >1) (minutes)* | Duration of complete motor blockade (score = 3) (minutes)* | Motor to analgesia time difference (minutes; $n = 6$)* |
|---|---|---|---|---|---|
| BUP | 0.25 | 1.8 ± 0.4 | 128 ± 100 (5) | 0 ± 0 (0) | 75 ± 80 |
| | 0.50 | 3.0 ± 0.0 | 238 ± 103 (6) | 65 ± 26 (6) | 103 ± 63 |
| | 0.75 | 3.0 ± 0.0 | 493 ± 112 (6) | 225 ± 45 (6) | 228 ± 155 |
| L-BUP | 0.25 | 1.7 ± 0.5 | 83 ± 70 (4) | 0 ± 0 (0) | 55 ± 46 |
| | 0.50 | 2.7 ± 0.5 | 183 ± 99 (6) | 28 ± 24 (4) | 103 ± 116 |
| | 0.75 | 2.8 ± 0.4 | 360 ± 128 (6) | 166 ± 113 (5) | 68 ± 73† |

Motor blockade score: 1 – normal motor response, 2 – partial motor block, and 3 – complete motor blockade. Data are expressed as mean ± SD.

*Number of animals out of six contributing to the data set are given in parentheses; mean values are also calculated from this data set; †significantly different from the same concentration of BUP ($p < 0.05$).

(Table 2). However, the difference was only significantly shorter with L-BUP 0.75% compared with BUP 0.75% ($p < 0.05$).

## Discussion

The local anaesthetic L-BUP is suitable for administration by the epidural route to dogs. Our results confirm that its overall analgesic effects in dogs were similar to those obtained with racemic BUP. In fact, in this study, its overall epidural analgesic potency was similar to that of BUP in the dog and, thus, its duration of action was also similar. As expected from studies in rats (Kanai et al. 1999) and humans (Cox et al. 1998; Burke et al. 1999; Faccenda et al. 2003), similar doses and concentrations (0.5–1.5 mg $kg^{-1}$) of either drug administered by the epidural route produced a similar and dose-dependent degree of analgesia and motor blockade. Also, BUP (Franquelo et al. 1995; Feldman et al. 1996) and L-BUP (Franquelo et al. 1999) had a fast onset of analgesic effect and motor blockade and the duration of their analgesia was similar, although the motor blockade tended to be shorter with L-BUP. However, our results also suggest an overall slightly lower analgesic effect of L-BUP, becoming statistically significant only with the middle dose and in the sacral and lumbar dermatomes, but not in the toenail base pinch response. This has also been reported in humans (Camorcia et al. 2005).

Epidural BUP is often referred to as the agent that is most likely to provide a differential block with the sensory block being more prevalent, which is the opposite of our results. These differential blocks are generally observed at low doses and concentrations (<0.25%) but not at higher doses/concentrations (Brennum et al. 1994) like those used in the present study. However, the duration of analgesia from a toe pinch outlasted the complete motor block with both BUP and L-BUP at all doses so the presence or absence of a differential block depends on the criteria used to judge the 'block'.

Reports on the relative durations of analgesia and motor blockade using BUP or L-BUP in humans are somewhat contradictory (Kopacz et al. 2000; Camorcia & Capogna 2003; Faccenda et al. 2003; Lacassie & Columb 2003). Clinical studies in humans (Foster & Markham 2000) suggested that the sensory blockade produced by L-BUP lasts longer, and this has been related to a greater vasoconstrictor action, especially at lower concentrations of the drug (Aps & Reynolds 1978). As in our study, the motor blockade produced in rats by L-BUP was shorter than the one produced by BUP (Kanai et al. 1999) although the opposite has been reported in dogs (Franquelo et al. 1999). However, the Franquelo et al. (1999) study focussed on the pharmacokinetic profile and was not designed to determine the analgesic effect of L-BUP; complete motor block was only assessed and employed to estimate the anaesthetic effect. Furthermore, the authors compared the duration of complete motor block between BUP and L-BUP using data obtained from two different experiments performed with different animals, whereas the present study compares both drugs in the same dogs. Also, the similar response to each drug at every studied dose/concentration further confirmed the similarity in their analgesic action. Despite the possibility of large individual variations and the small sample size, our data showed a similar overall action. Nevertheless, the analgesic effect and duration of L-BUP tended to be slightly less than that of BUP, but statistical confirmation of this trend would probably require more animals. Factors that might interfere with the observed effect include not only the dose and volume injected but also the size of the epidural space, the rate of injection, the exact position of the needle or catheter tip and the amount of epidural fat (Klide & Soma 1968).

Dose and volume are two key factors affecting the action of local anaesthetics. Common reported volumes for epidural injection vary between 0.14 and 0.22 mL $kg^{-1}$, and they provide a variable distribution of the drug within the epidural space (Feldman & Covino 1988). Such differences are directly linked to the level of effectiveness of the blockade where volumes of 0.22 mL $kg^{-1}$ of BUP 0.50% and 0.75% provided a block in the lumbar area in 80% of the dogs (Dermatomes $T_{13}$-$L_1$) (Heath et al. 1989; Duke et al. 2000) whereas smaller volumes of 0.14–0.15 mL $kg^{-1}$ of BUP 0.50% produced blockade in 30% (Duke et al. 2000) to 70% (Feldman & Covino 1988) of the dogs.

Time to onset of blockade was 5–10 minutes for BUP and L-BUP at a concentration of 0.50% and 0.75%; these times are similar to those previously reported for BUP (Feldman & Covino 1988; Duke et al. 2000; Gomez de Segura et al. 2000) and the duration of the dermatome blockade was highly dependent on the dermatome studied and the dose.

  

Recorded duration times for BUP may range from 90 minutes (1 mg $kg^{-1}$) up to 9 hours (2.5 mg $kg^{-1}$), although the testing method used, e.g., dermatome or toe pinch, or the duration of motor block, which is usually longer, or the co-administration of drugs such as adrenaline to prolong the duration of the analgesic effect, may also influence the results (Lebeaux 1973; Hendrix et al. 1996). However, pelvic limb block with BUP may last from 2 hours (Hurley et al. 1991; Duke et al. 2000) up to 4 or 6 hours (Heath et al. 1989), durations that are similar to those produced by L-BUP; the maximum dose administered in the present study was 1.5 mg $kg^{-1}$, and it provided analgesia (score ≥2) that lasted for up to 4 hours. A previous study comparing the analgesic action of BUP and ropivacaine in dogs (Duke et al. 2000) suggested a similar response to the two highest concentrations of BUP (0.50% and 0.75%). The difference between the two studies is probably due to the methods employed to measure blockade. Also, the intensity of the block varied with time, the data in the present work showed similar scores for the maximum analgesic effect although there are clinically significant dose-dependent differences in the duration of blockade. Therefore, although slight differences in the degree of analgesia were suggested from the results, clinically both drugs produced similar effects.

Although not an objective of this study, there were no overt signs of adverse effects produced by L-BUP or BUP given by the epidural route. Previous reports, also performed in dogs, found little or no changes in heart rate and arterial blood pressure following L-BUP (Franquelo et al. 1999) and BUP (Franquelo et al. 1995; Duke et al. 2000) administered IV or epidurally. Although L-BUP has less cardiac and CNS toxicity compared with BUP in many species, studies in dogs failed to demonstrate differences between BUP and L-BUP (Groban et al. 2000, 2002).

In conclusion, as previously observed in humans (Cox et al. 1998), epidural L-BUP in dogs caused a dose-dependent analgesia and motor blockade with an overall potency similar to that of BUP. Low doses (0.25%) had a weak and short-term (<30 minutes) analgesic effect but a higher dose produced a clinically useful analgesic effect with the highest dose producing a high degree of analgesia. The motor block was slightly shorter with epidural L-BUP than BUP although further clinical studies would be needed to determine whether this is clinically relevant.

## References


Aps C, Reynolds F (1978) An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. Br J Clin Pharmacol 6, 63–68.

Bardsley H, Gristwood R, Baker H et al. (1998) A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol 46, 245–249.

Brennum J, Nielsen PT, Horn A et al. (1994) Quantitative sensory examination of epidural anesthesia and analgesia in man; dose-response effect of bupivacaine. Pain 56, 315–332.

Burke D, Henderson DJ, Simpson AM et al. (1999) Comparison of 0.25% S(-)-bupivacaine with 0.25% RS-bupivacaine for epidural analgesia in labour. Br J Anaesth 83, 750–755.

Burm AG, van der Meer AD, van Kleef JW et al. (1994) Pharmacokinetics of the enantiomers of bupivacaine following intravenous administration of the racemate. Br J Clin Pharmacol 38, 125–129.

Camorcia M, Capogna G (2003) Epidural levobupivacaine, ropivacaine and bupivacaine in combination with sufentanil in early labour: a randomized trial. Eur J Anaesthesiol 20, 636–639.

Camorcia M, Capogna G, Columb MO (2005) Minimum local analgesic doses of ropivacaine, levobupivacaine, and bupivacaine for intrathecal labor analgesia. Anesthesiology 102, 646–650.

Cox CR, Faccenda KA, Gilhooly C et al. (1998) Extradural S(-)-bupivacaine: comparison with racemic RS-bupivacaine. Br J Anaesth 80, 289–293.

Duke T, Caulkett NA, Ball SD et al. (2000) Comparative analgesic and cardiopulmonary effects of bupivacaine and ropivacaine in the epidural space of the conscious dog. Vet Anaesth Analg 27, 13–21.

Faccenda KA, Simpson AM, Henderson DJ et al. (2003) A comparison of levobupivacaine 0.5% and racemic bupivacaine 0.5% for extradural anesthesia for caesarean section. Reg Anesth Pain Med 28, 394–400.

Feldman HS, Covino BG (1988) Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Anesth Analg 67, 1047–1052.

Feldman HS, Dvoskin S, Arthur GR et al. (1996) Antinociceptive and motor-blocking efficacy of ropivacaine and bupivacaine after epidural administration in the dog. Reg Anesth 21, 318–326.

Foster RH, Markham A (2000) Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 59, 551–579.

Franquelo C, Toledo A, Manubens J et al. (1995) Bupivacaine disposition and pharmacologic effects after intravenous and epidural administrations in dogs. Am J Vet Res 56, 1087–1091.

Franquelo C, Toledo A, Manubens J et al. (1999) Pharmacokinetics and pharmacologic effects of the S(-)

isomer of bupivacaine after intravenous and epidural administration in dogs. Am J Vet Res 60, 832–835.

Gomez de Segura IA, Vazquez I, De Miguel E (2000) Antinociceptive and motor-blocking action of epidurally administered IQB-9302 and bupivacaine in the dog. Reg Anesth Pain Med 25, 522–528.

Gristwood RW (2002) Cardiac and CNS toxicity of levobupivacaine: strengths of evidence for advantage over bupivacaine. Drug Saf 25, 153–163.

Groban L, Deal DD, Vernon JC et al. (2000) Ventricular arrhythmias with or without programmed electrical stimulation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine. Anesth Analg 91, 1103–1111.

Groban L, Deal DD, Vernon JC et al. (2002) Does local anesthetic stereoselectivity or structure predict myocardial depression in anesthetized canines? Reg Anesth Pain Med 27, 460–468.

Heath RB, Broadstone RV, Wright M et al. (1989) Using bupivacaine hydrochloride for lumbosacral epidural analgesia. Comp Cont Ed: Small Animal 11, 50–55.

Hendrix PK, Raffe MR, Robinson EP et al. (1996) Epidural administration of bupivacaine, morphine, or their combination for postoperative analgesia in dogs. J Am Vet Med Assoc 209, 598–607.

Huang YF, Pryor ME, Mather LE et al. (1998) Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg 86, 797–804.

Hurley RJ, Feldman HS, Latka C et al. (1991) The effects of epinephrine on the anesthetic and hemodynamic properties of ropivacaine and bupivacaine after epidural administration in the dog. Reg Anesth 16, 303–308.

Jones RS (2001) Epidural analgesia in the dog and cat. Vet J 161, 123–131.

Kanai Y, Tateyama S, Nakamura T et al. (1999) Effects of levobupivacaine, bupivacaine, and ropivacaine on tail-flick response and motor function in rats following epidural or intrathecal administration. Reg Anesth Pain Med 24, 444–452.

Kitchell RI, Evans HE (1993) The spinal nerves. In: Miller's Anatomy of the Dog. (3rd edn). Evans HE (ed.). WB Saunders, Philadelphia, USA. pp. 829–893.

Klide AM, Soma LR (1968) Epidural analgesia in the dog and cat. J Am Vet Med Assoc 132, 165–173.

Kopacz DJ, Allen HW, Thompson GE (2000) A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg 90, 642–648.

Lacassie HJ, Columb MO (2003) The relative motor blocking potencies of bupivacaine and levobupivacaine in labor. Anesth Analg 97, 1509–1513.

Lebeaux MI (1973) Experimental epidural anaesthesia in the dog with lignocaine and bupivacaine. Br J Anaesth 45, 549–555.

McLeod GA, Burke D (2001) Levobupivacaine. Anaesthesia 56, 331–341.

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