Pharmacokinetics of levobupivacaine 0.25% following caudal administration in children under 2 years of age

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Background. Levobupivacaine, the S(−)enantiomer of racemic bupivacaine is less cardiotoxic than racemic bupivacaine and the R(+)enantiomer dhexbupivacaine, while retaining similar local anaesthetic properties and potency to racemic bupivacaine. The pharmacokinetic profiles of the two bupivacaine enantiomers differs and that of racemic bupivacaine may be age dependent. We examined the pharmacokinetics of levobupivacaine after its single shot caudal epidural administration in children.

Methods. An open-label phase 2 study was undertaken to examine the pharmacokinetics of levobupivacaine 0.25% 2 mg kg⁻¹ in 49 children aged less than 2 yr, after single shot caudal epidural administration. Plasma concentrations were determined at intervals up to 60 min after caudal injection.

Results. Time to peak plasma concentration (Tmax) ranged between 5 and 60 min (median 30 min) and was reached later in children aged less than 3 months (P<0.005). Peak plasma concentration (Cmax) ranged between 0.41 and 2.12 µg ml⁻¹ (median 0.80, mean (SD) 0.91 (0.40) µg ml⁻¹).

Conclusion. After the caudal epidural administration of levobupivacaine 2 mg kg⁻¹ in children less than 2 yr of age, Cmax was within the accepted safe range for racemic bupivacaine. Tmax varied and occurred later in some children, particularly those aged less than 3 months. Sampling in future pharmacokinetic studies in this age group should extend beyond 60 min.

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Levobupivacaine is the S(−)enantiomer of racemic bupivacaine. Evidence suggests that it is less cardiotoxic than racemic bupivacaine and the R(+)enantiomer dhexbupivacaine, while retaining similar local anaesthetic properties and potency to racemic bupivacaine.¹ The two bupivacaine enantiomers have been demonstrated to differ in their pharmacokinetic profile.²³⁵

Previous studies have suggested that the pharmacokinetics of racemic bupivacaine administered by the caudal epidural route may be age dependent. Time to peak plasma concentration (Tmax) occurs later in children aged less than 6 months ¹⁶⁻¹¹ compared with older children. Ropivacaine, the N-propyl homologue of bupivacaine, has been shown to undergo slower absorption from the caudal epidural space in children than bupivacaine in children aged between 1 and 7 yr.¹⁰

No pharmacokinetic studies have been performed in children after the administration of levobupivacaine. This study aimed to examine the pharmacokinetics of levobupivacaine after its single shot administration into the caudal epidural space in children less than 2 yr of age.

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Patients and methods

This was an open-label phase 2 study conducted at two centres: Melbourne, Australia (centre 1) and Belfast, UK (centre 2). The study was performed under regulatory approval of the UK Department of Health Medicines Control Agency and the Australian Therapeutics Goods Administration and with the approval of the respective local ethics committees. Informed written consent was obtained from the parent or legal guardian of all patients entering the study. A total of 49 patients younger than 2 yr old undergoing circumcision, inguinal hernia repair, or orchiopexy and of ASA class I–II entered the study. Patients were excluded if they had severe renal, hepatic, respiratory or cardiac disease, neurological or neuromuscular disease, blood clotting disorders or dyscrasias, a history of seizure disorder, a known hypersensitivity to amide-type local anaesthetics, or any condition in which caudal analgesia is contraindicated. Patients were also excluded if they had received any vaccinations or investigational drugs within the previous 28 days.

Anaesthesia was induced with sevoflurane, oxygen, and nitrous oxide. No pre-medications were administered. Anaesthesia was maintained with halothane (end-tidal concentration 0.5 MAC) and nitrous oxide 70% in oxygen 30%. Breathing was spontaneous through either a facemask or a laryngeal mask. A caudal injection of levobupivacaine 0.25%, 2 mg kg⁻¹ was then administered before surgery. The time of completion of the injection was noted and taken as time zero.

Blood sampling

Serial blood samples were taken at pre-selected time points. Odd numbered patients had blood samples taken pre-caudal administration, and at 5, 15, 30, and 60 min after the administration of caudal levobupivacaine. Even numbered patients had blood samples taken pre-caudal, and at 10, 20, and 45 min after the administration of caudal levobupivacaine. Blood (1 ml) was aspirated from a peripherally sited cannula (not in use for i.v. fluid or concomitant medication administration) and stored for analysis. Before each sample was aspirated, 1 ml of blood was aspirated to eliminate dead space. After each sample was obtained, the dead space aspirate was re-transfused and the i.v. cannula then flushed with 1 ml of heparinized saline (10 u heparin ml⁻¹).

Blood samples were placed immediately into lithium heparin tubes and stored on ice, before being centrifuged within 60 min of collection. Plasma was separated, transferred into plastic tubes, and stored frozen at −20°C pending analysis.

Measurement of levobupivacaine concentration

An internal standard (10 μl of 20 μg ml⁻¹ prilocaine dissolved in methanol) was added to 1 ml of plasma. Saturated bicarbonate of soda (1 ml) was added and the samples mixed briefly before adding 6 ml of tertiary butyl ether and then mixing for 10 min. Samples were centrifuged (3000 r.p.m.) and the upper organic layer transferred to a clean tube and dried under a stream of nitrogen at 35°C. Each sample was reconstituted in 150 μl of high pressure liquid chromatography (HPLC) mobile phase (hexane: ethanol (85:15, v/v)) and analysed by HPLC–mass spectrometry. Samples (40 μl) were injected onto a Chiral 250 × 4.6 mm L-PGC CHI-L-PGC(B) 250 A column (Hichrom Ltd, Theale, Reading, Berkshire, UK) using a flow rate of 1 ml min⁻¹ and a column temperature of 40°C. Positive ion atmospheric pressure chemical ionization of HPLC eluent was performed using a Fisons Instruments VG Biotech Platform Mass Spectrometer (corona voltage 3.5 kV, cone voltage 15 V, source temperature 150°C, probe temperature 400°C). The assay was calibrated by using racemic bupivacaine (Chirocaine Ltd, Cambridge, UK) and the results were quantified by comparing peak area ratios of the samples to the calibration line using weighted (1/x) linear regression.

The assay’s limit of quantification was 0.01 μg ml⁻¹ and the coefficient of variation at this limit, 5.7%. All data were reported to the nearest 0.01 μg ml⁻¹. Drug concentrations were expressed in terms of levobupivacaine (freebase equivalents).

Pharmacokinetic analysis

The observed peak plasma concentration (C_max) and the time it was reached (T_max) were recorded for each patient.

Statistical analysis

The Wilcoxon rank sum test was used to test the data generated hypothesis that T_max was prolonged in infants aged less than 3 months. A non-parametric test was used as non-linear and fixed sampling times had been used.

Results

In total, 49 patients were recruited into the study and received levobupivacaine (33 patients at centre 1 and 16 at centre 2). One patient was withdrawn from the study because of a technical failure whilst performing the caudal epidural and no blood samples were taken. Of the remaining 48 patients, 11 were aged less than 3 months and 37 aged 3 months or more.

Of the intended 221 blood samples, 199 were obtained. In 35 patients, all intended blood samples were aspirated. In the remainder of patients, aspiration of blood from the i.v. cannula was not possible at various time points. Only the initial sample (time zero) was taken in the patient in whom technical failure of the caudal epidural occurred. One patient was excluded from any pharmacokinetic analysis as the time zero sample registered greater than zero (clerical
error). All but two patients where blood sampling was incomplete \((n=12)\) were excluded from \(T_{\text{max}}\) analysis. \(T_{\text{max}}\) and \(C_{\text{max}}\) analysis were conducted in these two patients as \(C_{\text{max}}\) was reached before blood sampling was unsuccessful.

\(T_{\text{max}}\) ranged from 5 to 60 min, median 30 min (Fig. 1). \(T_{\text{max}}\) occurred at the time of the final sample time point (45 or 60 min) more often in patients aged less than 3 months \((P<0.005)\). In the nine patients aged less than 3 months in whom all intended blood samples were obtained, \(C_{\text{max}}\) was reached at the time of the last sample in all but one patient \((88.9\%)\), in whom \(T_{\text{max}}\) occurred at 15 min. In patients aged 3 months or more in whom \(C_{\text{max}}\) was reached \((26\) with full data sets and the two patients in whom \(C_{\text{max}}\) was reached but in whom the last data point \((60\) min) was missing), \(T_{\text{max}}\) (median 20 min) was reached before the time of the last sample in 20/28 \((71.4\%)\) patients.

\(C_{\text{max}}\) in patients less than 3 months \((n=9)\) ranged from 0.59 to 1.38 \((\text{mean 0.97, (SD 0.27) } \mu\text{g ml}^{-1})\). In patients greater than/equal to 3 months of age \((n=28)\), \(C_{\text{max}}\) ranged from 0.42–2.12 \((\text{mean 0.94, (SD 0.41) } \mu\text{g ml}^{-1})\). When patients without full data sets were included, \(C_{\text{max}}\) range was 0.42–2.12 \(\mu\text{g/ml}\) (median 0.80, mean \((\text{SD}) 0.91 (0.40) \mu\text{g ml}^{-1}\), for all patients, with mean 1.02 \((\text{SD 0.43) in those less than 3 months and 0.88 (SD 0.34) in those greater than/ equal to 3 months}).

**Discussion**

This is the first study describing the pharmacokinetic profile of levobupivacaine in children. Our results demonstrate that time to \(T_{\text{max}}\) varies considerably and is more likely to be reached later in infants aged less than 3 months. In those less than 3 months of age and in whom all intended samples were drawn, the last blood sample drawn corresponded to the highest recorded plasma concentration in eight of nine patients. \(T_{\text{max}}\) (actual) may not have been reached, potentially underestimating \(C_{\text{max}}\) and the difference in \(T_{\text{max}}\) that we observed between this group and those older than 3 months of age.

In contrast, \(C_{\text{max}}\) was observed before the final sample in 21/28 patients aged greater than/equal to 3 months with \(T_{\text{max}}\) occurring between 5 and 30 min (median 20 min).

The longer \(T_{\text{max}}\) observed in children less than 3 months of age could be attributed to slower absorption of levobupivacaine from the epidural space (consistent with the longer absorption half-life observed in this group) and/or reduced clearance. The vascularity and fat content of the epidural space and the ability of neonates and young infants to clear drugs are known to alter with age.\(^{12}\)

Other investigators have published pharmacokinetic studies after the caudal administration of plain racemic bupivacaine in children. Only two other studies have included patients less than 3 months of age. In one of these, 13 infants less than 6 months of age were studied.\(^{11}\) \(T_{\text{max}}\) was 10–40 (median 27.5) min in the six infants less than 3 months of age, and 20–60 (median 20) min in the seven infants aged between 3 and 6 months. In the other study, data for seven infants less than 5 months of age were reported.\(^{8}\) Four were less than 3 months post-conceptual age. A wide range for \(T_{\text{max}}\) was reported in the plain bupivacaine group (30–240 min, median 60 min); however, it was not possible from the data presented to examine \(T_{\text{max}}\) separately in those less than 3 months of age.

It is important to bear in mind the longer time to \(T_{\text{max}}\) in neonates, given the trend to using higher doses of local anaesthetics via the caudal epidural route for short surgical procedures.\(^{13}\) It has been demonstrated in young pigs that bupivacaine toxicity is age dependent and affected by volatile anaesthetic agents.\(^{14}\) Although evidence suggests levobupivacaine is less cardiotoxic, we have no idea at what plasma concentrations children are at risk of toxicity.

Compared with racemic bupivacaine, levobupivacaine may also take longer to reach \(T_{\text{max}}\) in older children although the sampling interval protocol used in this and other studies together with the cessation of sampling at either 45 or 60 min in our study, make it difficult to be certain. \(T_{\text{max}}\) was reached at 5–60 min (median 20 min, mean 27.7 \((\text{SD 15.1})\) min) in the 28 patients greater than/equal to 3 months. Other studies have demonstrated similar mean times to \(T_{\text{max}}\), but within a narrower range. These studies\(^{7–10}\) have reported means \((\text{SD})\) \([\text{range}]\) of 29 \((3) [19.7–38.4]\) min, 27 \([10–40]\) min, 29.6 \((7.9)\) min and a median of 20 min \([15–50]\) min, respectively. All except the study by Karmaker and co-workers\(^{16}\) \((1–7\) yr) were performed in children more than 2 yr and all were limited by the use of small sample sizes, which given the degree of variation observed, limits any conclusions.
Levobupivacaine may have vasoconstrictor properties that account for the prolongation in $T_{\text{max}}$ observed in our study. Local anaesthetics are known to exert vasoactive effects on blood vessels. Levobupivacaine has been reported to cause more vasoconstriction than dextubupivacaine in subclinical concentrations\textsuperscript{15} and ropivacaine is reported to have vasoconstrictor properties.\textsuperscript{16} Studies comparing the caudal administration of ropivacaine and racemic bupivacaine in older children have observed $T_{\text{max}}$ to be longer with ropivacaine.\textsuperscript{8,10,17}

$T_{\text{max}}$ occurred at 5 min in one of our patients and the highest $C_{\text{max}}$ recorded in this study (2.12 $\mu$g ml$^{-1}$) was in that same patient. It is likely that a partial intravascular injection of LA occurred in this patient. Neither ECG changes nor any other indications of local anaesthetic toxicity were observed. Interestingly, other studies examining the pharmacokinetics of local anaesthetic drugs after caudal administration in children have also observed $T_{\text{max}}$ to occur at 10 min or less in just one patient.\textsuperscript{8,10,11,18–20} It is conceivable that inadvertent partial intravascular injection occurs more commonly than realized clinically, supporting the use of long acting local anaesthetics with an improved safety profile compared with racemic bupivacaine.

The mean $C_{\text{max}}$ in this study (0.91 (SD 0.40) $\mu$g ml$^{-1}$) was higher, and its inter-individual variability greater than in previous investigations where the same total dose of caudal epidural racemic bupivacaine (2 mg kg$^{-1}$) was administered to children. Previous studies\textsuperscript{8,10,17} measured $C_{\text{max}}$ in children ranging in age from 0.6 to 8.7 yr and reported mean (SD) values of 0.57 (0.1), 0.802 [range 0.408–1.284], 0.73 (0.23) and 0.57 (0.17) $\mu$g ml$^{-1}$, respectively. In these studies, racemic bupivacaine was administered in a larger volume (0.2% solution).

Other investigators\textsuperscript{6,7,21} have studied the pharmacokinetics of racemic bupivacaine after caudal administration in neonates, infants and children using a higher dose (2.5 mg kg$^{-1}$) but a similar concentration to that used in this study. The mean (SD) $C_{\text{max}}$ reported in these studies were 1.25 [range 0.96–1.64], 0.80 (0.45) and 1.109 [range 0.607–2.195] $\mu$g ml$^{-1}$, respectively.

Enantiomer selective pharmacokinetics could explain why the $C_{\text{max}}$ of levobupivacaine was higher than that observed after the same dose of racemic bupivacaine after caudal epidural administration. The plasma concentration of levobupivacaine has been reported previously to be higher than that of dextubupivacaine in both animal\textsuperscript{22} and human\textsuperscript{15} studies after the administration of racemic bupivacaine. This was attributed to differential protein binding of the two enantiomers (levobupivacaine is more bound).\textsuperscript{5}

No recommendations exist regarding the ‘safe’ plasma concentration of levobupivacaine in children. Although arterial concentrations are more important than venous with regards toxicity, ethical constraints, especially in paediatric studies, necessitate measures of venous concentration. For racemic bupivacaine, the mean venous total plasma concentration at which adult volunteers reported signs of central nervous system toxicity was 2.1 mg ml$^{-1}$.\textsuperscript{23} However, extrapolation from racemic bupivacaine studies performed in adults may not be valid given the free fraction differential between dext- and levobupivacaine and reduced plasma protein binding concentrations in neonates and young infants. In addition, regional pharmacokinetic and pharmacodynamic differences exist between the two bupivacaine enantiomers such that dextubupivacaine is more likely to result in cardiotoxicity.

In conclusion, we have demonstrated that after the administration of 2 mg kg$^{-1}$ levobupivacaine into the caudal epidural space of children less than 2 yr of age, the time at which peak plasma concentration occurs varies considerably. In some children, particularly those aged less than 3 months, $T_{\text{max}}$ occurs later. In order to further describe the pharmacokinetics of caudally administered levobupivacaine, blood sampling should extend well beyond 60 min after its administration. Future studies examining local anaesthetic pharmacokinetics should investigate the differential kinetics between children aged less than and those greater than 3 months of age and should include measurement of free and total local anaesthetic plasma concentrations.

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