Regional Anaesthesia

Pharmacokinetics of levobupivacaine after caudal epidural administration in infants less than 3 months of age

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Background. There are few data describing levobupivacaine pharmacokinetics in infants (<3 months) after caudal administration.

Methods. An open-label study was undertaken to examine the pharmacokinetics of levobupivacaine 2.5 mg ml⁻¹, 2 mg kg⁻¹ in children aged less than 3 months after single-shot caudal epidural administration. Plasma concentrations were determined at intervals from 0.5 to 4 h after injection. A population pharmacokinetic analysis of levobupivacaine time–concentration profiles (84 observations) from 22 infants with mean postnatal age (PNA) 2.0 (range 0.6–2.9) months was undertaken using non-linear mixed effects models (NONMEM). Time–concentration profiles were analysed using a one-compartment model with first-order input and first-order elimination. Estimates were standardized to a 70 kg adult using allometric size models.

Results. Population parameter estimates (between-subject variability) for total levobupivacaine were clearance (CLt) 12.8 (coefficient of variation (CV) 50.6%) litre h⁻¹ 70 kg⁻¹, volume of distribution (Vt) 202 (CV 31.6%) litre 70 kg⁻¹, absorption half-life (Tabs) 0.323 (CV 18.6%) h 70 kg⁻¹. Estimates for the unbound drug were clearance (CLfree) 104 (CV 43.5%) litre h⁻¹ 70 kg⁻¹, volume of distribution (Vfree) 1700 (CV 44.9%) litre 70 kg⁻¹, absorption half-life (Tabsfree) 0.175 (CV 83.7%) h 70 kg⁻¹. There was no effect attributable to PNA on CL or V. Time to peak plasma concentration (Tmax) was 0.82 (CV 18%) h. Peak plasma concentration (Cmax) was 0.69 (CV 25%) mg ml⁻¹ for total levobupivacaine and 0.09 (CV 37%) mg ml⁻¹ for unbound levobupivacaine.

Conclusions. Clearance in infants is approximately half that described in adults, suggesting immaturity of P450 CYP3A4 and CYP1A2 enzyme isoforms that metabolize levobupivacaine in infants. This lower clearance delays Tmax, which was noted to occur approximately 50 min after administration of caudal epidural levobupivacaine.

Keywords: anaesthetic techniques, regional, caudal; anaesthetics local, levobupivacaine; infants; neonates; pharmacokinetics, levobupivacaine

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A previous study describing the pharmacokinetics of levobupivacaine 2.5 mg ml⁻¹, 2 mg kg⁻¹ after caudal administration in children younger than 2 yr suggested that the time to peak plasma concentration (Tmax) was reached later in children aged <3 months.¹ That study may have underestimated the peak plasma concentration (Cmax) and Tmax because blood was sampled only up to 60 min after levobupivacaine administration. These confounded parameters (Cmax, Tmax) are valuable tools that give us an overview of time–concentration profiles after administration of a drug. However, they depend very much on when samples are taken. If few samples are taken or if samples are missing, accuracy disappears. Knowledge of the true pharmacokinetic parameters (absorption rate constant [KA], volume of distribution [V], clearance [CL]) allows us to predict the profile for a typical individual and estimate confounded parameters with greater precision.
This study was performed to overcome the limitations of the previous report and aimed to describe the pharmacokinetics of levobupivacaine after single-shot administration into the caudal epidural space in infants <3 months of age. This analysis further investigates and quantifies the effect of age using a population-based approach that included size as the primary covariate in an effort to disentangle age-related from size-related factors.

Methods

After approval from the Royal Children’s Hospital Ethics Committee, written informed consent was obtained from a parent or legal guardian for their child to enter the study. Levobupivacaine is licensed for use in children >6 months of age in Australia and hence this study constituted an off-label use of the drug, which was approved by the Hospital Ethics Committee. Infants of <3 months postnatal age and ASA class I or II undergoing subumbilical surgery were eligible. Exclusion criteria were previous hypersensitivity to racemic bupivacaine or levobupivacaine, blood clotting disorders, local skin infection over the sacral hiatus or myelomeningocele.

No premedication was administered. Anaesthesia was induced with sevoflurane, oxygen and nitrous oxide. Anaesthesia was maintained with isoflurane (end-tidal concentration 0.7 MAC) and nitrous oxide 70% in oxygen 30%. Breathing was spontaneous through either a laryngeal mask or a face mask. All caudal injections were performed using a 23 gauge hypodermic needle, which was introduced via the sacrococcygeal membrane. After careful aspiration, a caudal injection of levobupivacaine 2.5 mg ml\(^{-1}\), 2 mg kg\(^{-1}\) was administered over 30 s before commencement of surgery. The time of completion of the injection was recorded as time zero.

Serial blood samples were taken 30, 60, 120, 180 and 240 min after the caudal administration of levobupivacaine. Blood (1 ml) was aspirated from a peripherally sited dedicated 22-G or 24-G i.v. cannula (not in use for i.v. fluid or concomitant medication administration). One millilitre of blood was aspirated from the cannula before sampling to eliminate dead space. After each sample had been obtained, the dead-space aspirate was retransfused and the i.v. cannula then flushed with 1 ml of heparinized saline (heparin 10 units ml\(^{-1}\)). If blood could not be aspirated from the i.v. cannula after emergence from anaesthesia, the cannula was not replaced unless clinically indicated. Blood samples were placed immediately into lithium heparin tubes, before being centrifuged within 60 min of collection. Plasma was separated, transferred into plastic tubes and stored at \(-20^\circ\text{C}\) pending analysis.

Plasma 0.2 ml, H\(_2\)O 0.2 ml or standard levobupivacaine solution, 0.05 ml, 15 mg litre\(^{-1}\) mepivacaine (internal standard) and 6 ml ethyl acetate were combined in a borosilicate glass tube. The tubes were capped, vortexed for 10 s and centrifuged at 1000 \(\text{g}\) for 5 min. The ethyl acetate phase was transferred to a second borosilicate tube and evaporated to dryness under nitrogen at \(40^\circ\text{C}\). The residue was reconstituted in 0.025 ml methanol, with the entire sample injected into the gas chromatograph.

The unbound concentration was determined after ultrafiltration of 0.5 ml plasma using the MPS-1 micropartition system using YMT membranes (Amicon) at room temperature. The ultrafiltrate was extracted as for plasma.

The chromatograph used a programmable temperature vaporizer, a 30 m\(\times\)0.25 mm BPX50 column (SGE), and nitrogen–phosphorus detection. The method is linear to at least 2000 ng ml\(^{-1}\), with a limit of quantitation of 5 ng ml\(^{-1}\) (coefficient of variation [CV]=12%) and a CV of 4.4% at 200 ng ml\(^{-1}\) (\(n=8\)).

Free (unbound) concentration was estimated in one sample from each subject and unbound concentrations were predicted from this unbound percentage.

Pharmacokinetic analysis

A one-compartment model with first-order input and first-order elimination was used. Population parameter estimates were obtained using a non-linear mixed effects model (NONMEM).\(^2\) This model accounts for population parameter variability (between and within subjects) and residual variability (random effects) as well as parameter differences predicted by covariates (fixed effects). The population parameter variability in model parameters was modelled by a proportional variance model. An additive term characterized the residual unknown variability. This error model assumes that the residual variability is the same order of magnitude over the whole range of measurements. The population mean parameters, between-subject variance and residual variance were estimated using the first-order conditional estimate method using ADVAN 2 TRANS 2 of NONMEM V. Convergence criterion was three significant digits. The covariance of clearance and distribution volume variability was incorporated into the model. A Compaq Digital Fortran Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel, Santa Clara, CA, USA) under Microsoft Windows XP (Microsoft, Seattle, WA, USA) was used to compile and execute NONMEM.

The parameter values were standardized for a body weight of 70 kg using an allometric model:\(^3\)\(^4\)

\[
P_i = P_{\text{std}} \times \left(\frac{W_i}{W_{\text{std}}}\right)^{PWR}
\]

where \(P_i\) is the parameter in the \(i\)th individual, \(W_i\) is the weight in the \(i\)th individual and \(P_{\text{std}}\) is the parameter in an individual with a weight \(W_{\text{std}}\) of 70 kg. This standardization allows comparison of neonatal parameter estimates with those reported for adults. The PWR exponent was 0.75 for clearance and 1 for distribution volumes.\(^5\)\(^7\)

The quality of fit of the pharmacokinetic model to the data was sought by NONMEM’s objective function and by visual
examination of plots of observed vs predicted concentrations. Models were nested and an improvement in the objective function was referred to the $\chi^2$ distribution to assess significance, e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha=0.05$.

The parameter estimates and their variance were used to simulate a time–concentration profile for total levobupivacaine 2.5 mg ml$^{-1}$ after a caudal dose of 2 mg kg$^{-1}$. The population predicted mean profile and 5th and 95th centiles were calculated from 1000 simulated profiles.

Cmax (peak concentration) and Tmax (time to peak concentration) were calculated based on individual Bayesian parameter estimates. The following equations were used:

$$T\text{max}=\ln(\frac{KA}{K})/(KA-K)$$

$$C\text{max}=\text{dose} \times KA/[V \times (KA-K)]$$

$$\times \exp(-K \times T\text{max}) - \exp(-KA \times T\text{max})$$

where Ln is the natural logarithm, KA is the absorption rate constant (equivalent to Ln(2)/Tabs; Tabs is the absorption half-life), K is the elimination rate constant and exp the exponential function.

**Results**

Patient characteristics are shown in Table 1. There were 84 plasma samples obtained from 22 infants. All intended blood samples were aspirated in 12 subjects. In the remainder, aspiration of blood from the i.v. cannula was not possible at various time points. Three of the intended five samples were obtained in three patients and one or two samples in the remainder. The operation type was inguinal hernia repair in all but four patients; two of these had colostomy formation, one had circumcision and one had incision and drainage of perineal abscess.

Parameter estimates are shown in Table 2. Observed time–concentration profiles and the population prediction profile for total and unbound data sets are shown in Figure 1. The population predicted mean profile and 5th and 95th centiles calculated from 1000 simulated profiles are incorporated into Figure 1. The correlation of between-subject variability (BSV) for CL and V was 0.59, CL and absorption half-life (Tabs) 0.99 and V and Tabs 0.68. There was no effect of postnatal age on clearance or volume (Fig. 2A and B) over the age range studied. Figure 3A–C demonstrates the quality of fit for pharmacokinetic data from the total levobupivacaine data set. Individual concentration predictions are based on values of maximum a posteriori Bayesian estimates of the parameters while predicted population concentrations are based on population parameters and covariate information.

In patients where all intended samples were aspirated, levobupivacaine total Cmax ranged between 0.4 and 1.2 (mean 0.72, SD 0.23) μg ml$^{-1}$. The highest levobupivacaine total plasma concentration recorded in any patient was 1.2 μg ml$^{-1}$. The measured unbound levobupivacaine fraction ranged between 0.054 and 0.20 (mean 0.13, SD 0.04). The mean estimated Tmax, based on parameter estimates for each individual, was 0.82 h (CV 18%) (Fig. 4). The mean estimates for Cmax were 0.69 μg ml$^{-1}$ (CV 25%) for total levobupivacaine and 0.09 μg ml$^{-1}$ (CV 37%) for unbound levobupivacaine. A trend line shows a decrease of Tmax with age, but data were too few to confirm this trend.

**Discussion**

This study describes the pharmacokinetic profile of levobupivacaine in infants <3 months of age. We report levobupivacaine pharmacokinetic parameters in infants using size as a primary covariate. The estimates for clearance (12.8 litre h$^{-1}$ 70 kg$^{-1}$; CV 50.6%) are approximately half that described in adults (20.9 [SD 6.8] litre h$^{-1}$ 70 kg$^{-1}$).^5^ Volume of distribution is greater than in adults (Vss 56 litre 70 kg$^{-1}$ [SD 14]),^6^ consistent with similar observations for bupivacaine. Size has considerable impact on the estimation and interpretation of pharmacokinetic parameters in children and is often unaccounted for in neonatal and infant

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<tr>
<td>Postnatal age: mean (SD, range)</td>
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<td>Gestational age: mean (SD, range)</td>
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<td>Weight: mean (SD, range)</td>
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<td>Gender (n=22)</td>
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| Table 2 Parameter estimates for total and unbound levobupivacaine pharmacokinetics using both the allometric and per kilogram size models. BSV is between-subject variability; se is the standard error of the estimate |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Allometric (70 kg) | BSV (%) | se (%) | Per kg | BSV (%) | se (%) |
| Total levobupivacaine |
| CL | 12.8 litre h$^{-1}$ | 50.6 | 10.1 | 0.377 litre h$^{-1}$ | 51.2 | 11.5 |
| V | 202 litre 70 kg$^{-1}$ | 31.6 | 7.9 | 2.87 litre | 31.2 | 8.0 |
| Tabs | 0.323 h 70 kg$^{-1}$ | 18.6 | 47.7 | 0.164 h | 15.2 | 13.5 |
| Residual error | 0.07 mg litre$^{-1}$ | 17.1 | 32.1 |
| Unbound levobupivacaine |
| CL | 104 litre h$^{-1}$ 70 kg$^{-1}$ | 43.5 | 17.4 | 3.1 litre h$^{-1}$ | 42.5 | 17.0 |
| V | 1700 litre 70 kg$^{-1}$ | 44.9 | 10.4 | 24.1 litre | 45.1 | 10.5 |
| Tabs | 0.175 h 70 kg$^{-1}$ | 83.7 | 57.7 | 0.095 h | 82.2 | 58.7 |
| Residual error | 0.01 mg litre$^{-1}$ | 33.4 | 33.4 |
Levobupivacaine pharmacokinetics in infants

Fig 1 Time–total levobupivacaine concentration profiles for each patient, with the mean population predicted profile in bold. The dotted lines represent the 5th and 95th centiles calculated from 1000 simulated profiles.

Fig 2 (a) Individual predicted total levobupivacaine clearances (CL), standardized to a 70-kg person, from the NONMEM post hoc step, are plotted against postnatal age. (b) Individual predicted volumes of distribution (V), standardized to a 70-kg person, from the NONMEM post hoc step, are plotted against postnatal age. Neither CL nor V is related to infant age within the age range studied.

pharmacokinetic studies. A great many physiological, structural and time-related variables scale predictably within and between species, with weight exponents of 0.75, 1 and 0.25 respectively. We have used these ‘1/4 power models’ in the present study rather than centred weight, or some other function of weight, because the 1/4 power models have sound biological principles. West and colleagues have used fractal geometry to mathematically explain this phenomenon. The 3/4 power law for metabolic rate was derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes. These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms.
Fig 3 Quality of fit of total levobupivacaine pharmacokinetic data. (A) Population predictions are compared with observed data. The line $x=y$ is the line of identity. (B) Individual Bayesian concentration predictions based on values of the parameters for the specific individual are compared with observed data. (C) The weighted residuals for each subject with values for each subject joined by vertical bars.

Fig 4 Estimated values for $T_{max}$, based on parameter estimates for each individual. $T_{max}$ tended to decrease with age.
By choosing weight as the primary covariate, the secondary effects of postnatal age could be investigated. We were unable to demonstrate an effect of age within this current cohort because of small sample size limited to a narrow age range. 

Clearance in this cohort of infants was reduced compared with adults, but the time course of maturation could not be quantified. Levobupivacaine is metabolized by the CYP3A4 and CYP1A2 isoforms to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. Data from ropivacaine, an amide anesthetic that is metabolized by these same enzymes, suggests that clearance approaches adult values within the first 6–12 months of life. 

Tmax after single-shot caudally administered levobupivacaine is reached later in young infants. The absorption half-life is similar to that described after paediatric epidural bupivacaine (0.33 h), suggesting that reduced clearance contributes to a delayed Tmax. The impact of caudal space vascularity, epidural fat or caudal absorptive surface area differences between infants and older children is undefined. Age did not affect the disposition or systemic absorption of bupivacaine in 20 adult male patients aged 22–81 yr. 

Levobupivacaine is highly bound to α1 acid glycoprotein (AAG). AAG is an acute-phase reactant that increases after surgical stress. Mean preoperative AAG concentrations reduced clearance rather than AAG concentration. Weations observed during long-term epidural is attributable to these same enzymes, suggests that clearance approaches similar to that described after paediatric epidural bupivacaine in 20 adult male patients aged 22–81 yr.

In conclusion, we have demonstrated that the clearance of levobupivacaine after single-shot caudal administration in infants <3 months of age is approximately half that described in adults, suggesting immaturity of P450 CYP3A4 and CYP1A2 enzyme isoforms that metabolize levobupivacaine. This lower clearance delays Tmax, which was noted to occur approximately 50 min after administration of caudal levobupivacaine. Plasma concentrations achieved suggest that 2 mg kg⁻¹ levobupivacaine administered via the caudal route as a single dose is safe to use in this age group. We were unable to detect a relationship between postnatal age and clearance of levobupivacaine in this population.

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