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Levobupivacaine plasma concentrations following repeat caudal anaesthetics

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Key Words: levobupivacaine; Anesthesia, Caudal; pharmacokinetics; infant; local anesthetic, toxicity

What is already known about this subject:

Total plasma concentrations of levobupivacaine in infants who have received single caudal anaesthetics are reported below the lower limit of concentrations associated with local anaesthetic systemic toxicity.

Infants less than three months of age however have slower epidural absorption time, higher maximum plasma concentrations and longer times to peak concentration due to reduced clearance. There are few studies reporting total plasma concentrations of levobupivacaine after repeat caudal bolus doses.

What this study adds:

Repeat caudal dosing of levobupivacaine in infants aged 3-6 months, produces total drug concentrations below the lower limit of concentrations associated with local anaesthetic neuro and cardiac systemic toxicity. Pharmacokinetic modelling and simulations to determine total plasma levobupivacaine concentration support repeat caudal levobupivacaine (2.5 mg kg^{-1}) at three or four hours after the initial caudal block (2.5 mg kg^{-1}) in infants 3-6 months of age and older children.

Abstract

Aim: A single caudal anaesthetic at the start of lower abdominal surgery is unlikely to provide prolonged analgesia. A second caudal at the end of the procedure extends the analgesia duration but total plasma concentrations may be associated with toxicity. Our aim was to measure total plasma levobupivacaine concentrations after repeat caudal anaesthesia in infants and to generate a pharmacokinetic model for prediction of plasma concentrations after repeat caudal anaesthesia in neonates, infants and children.

Methods: Infants undergoing definitive repair of anorectal malformations or Hirschsprung's disease received a second caudal anaesthesia at the end of the procedure. Total levobupivacaine concentrations were assayed 3-4 times in the first 6 hours after the initial caudal. These data were pooled with data from four studies describing plasma concentrations after levobupivacaine caudal or spinal anaesthesia. Population pharmacokinetic parameters were estimated using non-linear mixed-effects models. Covariates included postmenstrual age and body weight. Parameter

estimates were used to simulate concentrations after a repeat levobupivacaine 2.5 mg kg^{-1} caudal at 3 or 4 hours following an initial levobupivacaine 2.5 mg kg^{-1} caudal.

Results: Twenty one infants (postnatal age 11-32 weeks, gestation 37-39 weeks, weight 5.2-8.6 kg) were included. The measured peak plasma concentration after repeat caudal levobupivacaine 2.5 $mg.kg^{-1}$ four hours after initial caudal was 1.38 $mg.L^{-1}$ (95% prediction interval 0.60-2.6 $mg.L^{-1}$) and three hours after initial caudal was 1.46 $mg.L^{-1}$ (0.60-2.80) $mg.L^{-1}$. Simulation of total plasma concentrations in neonates (7 kg, 57 weeks postmenstrual age) given caudal levobupivacaine four hours after the initial caudal were 1.76 $mg.L^{-1}$ (0.68-3.50) $mg.L^{-1}$ if 2.5 $mg.kg^{-1}$ levobupivacaine was used and 0.88 $mg.L^{-1}$ (0.34-1.73) $mg.L^{-1}$ if 1.25 $mg.kg^{-1}$ of 0.125% levobupivacaine was used. In simulated older children (20 kg,6 years) the mean maximum concentration was 1.43 $mg.L^{-1}$ (0.60-2.70) $mg.L^{-1}$ if 2.5 $mg.kg^{-1}$ levobupivacaine was repeated at 3 hours.

Conclusion: Repeat caudal levobupivacaine 2.5 $mg.kg^{-1}$ at 3 hours after an initial 2.5 $mg.kg^{-1}$ dose does not exceed the concentration associated with systemic local anaesthetic toxicity. In 2.5% of simulated neonates (weight 3.8kg,PMA 40 weeks) repeat caudal anaesthesia demonstrates broaching of the lower concentration limit associated with toxicity at both three and four hours after initial caudal.

1. Introduction:

A caudal anaesthetic at the start of the procedure is unlikely to provide prolonged postoperative analgesia in infants undergoing abdominal surgery such as definitive repair of anorectal anomalies or Hirschsprung's disease[1]. A second caudal at the end of the procedure extends the analgesia into the recovery phase but may be associated with excess total plasma concentrations if the interval between caudal boluses is short. Previous papers reporting total levobupivacaine

plasma concentrations after single caudal anaesthesia in children less than 2 years of age describe low plasma concentrations overall but there was reduced clearance in infants younger than 3 months of age. Immaturity of the cytochrome CYP 3A4 and CYP 1A2 isoforms that metabolise levobupivacaine result in delayed time at which maximum concentration (T max) and increased maximum concentration (Cmax) but no overt episodes of local anaesthetic toxicity have been reported[2,3]. Levobupivacaine neuraxial absorption and clearance values have been reported but the studies cover a limited cohort age range and limited duration of sampling after the initial caudal and have used postnatal age (PNA) rather than postmenstrual age (PMA) that better reflects clearance maturation [4]. There are no studies that report the plasma levobupivacaine concentrations associated with repeat caudal boluses.

The aim of this study was to measure total plasma concentrations in infants undergoing lower abdominal surgery and combine this with data from other levobupivacaine studies to generate a neuraxial pharmacokinetic model which could then be used to predict levobupivacaine plasma concentrations at variable intervals after the initial caudal in neonates infants and older children[5,6].

2. Methods

2.1. Study Design

This was a single-centre, prospective, open-label study. Infants undergoing definitive repair of anorectal malformation or Hirschsprung's disease who received a second caudal anaesthetic were studied. All received an initial caudal anaesthetic of 2.5 $mg.kg^{-1}$ levobupivacaine 0.25% . At the completion of surgery infants received a second caudal local anaesthetic dose of 2.5 $mg.kg^{-1}$ 0.25% levobupivacaine. Blood samples (2.5 mL) were taken from a central venous catheter placed for the surgery. Plasma total concentrations were determined at intervals from

30 minutes after the first caudal administration, immediately prior to the second caudal and at intervals from 30-140 minutes after the second caudal.

2.2. Ethics Approval: The study protocols were approved by the Royal Childrens Hospital human ethics committee (HREC/56238/RCHM-2019) and written informed consent was obtained from the parents or legal guardians.

2.3. Assay Methodology

High-performance liquid chromatography (HPLC) was used for levobupivacaine assay. A measured volume of plasma (100 to 1000 µL) was added to a methanol-rinsed culture tube with 50 µL 15 mg/L mepivacaine (internal standard) along with 1.5 mL 0.5 M Na_3PO_4 and 5 mL ethyl acetate. After the mixture is vortex mixed and centrifuged at 2200 G, the ethyl acetate layer is transferred to a second tube and evaporated to dryness under a stream of nitrogen gas at room temperature. The residue is reconstituted in 100 µL of HPLC mobile phase and up to 100 µL injected onto the column for analysis. The HPLC instrument is made up of a Waters Model 510 pump, Bio-Rad AS-100 auto sampler and Waters Model 450 UV absorbance detector, operated at 210 nm. The HPLC column is a 15 cm x 3.9 mm Waters Symmetry C18 (5 µ particle size) with a mobile phase of 58% acetonitrile in 50 mM KH_2PO_4 (pH 6.9), running at 1 $mL.min^{-1}$. The accuracy (bias %) was 4.1% (-1.5 to 5.8%) and precision (coefficient of variation) was 4.9% (1.4-3.1%) at 0.2 $mg.L^{-1}$. The method is linear to at least 5 $mg.L^{-1}$, with a limit of quantitation of 0.02 $mg.L^{-1}$.

2.4.Pharmacokinetic analysis

2.4.1. Data

i) ***Current data.*** Plasma concentrations were measured in infants receiving a second caudal anaesthetic. The cohort involved 21 patients [PMA 59 weeks (range 49-70), weight 6.9 (5.2-8.6) kg] and 80 observations

ii) ***Pooled data.*** Data was pooled from four studies describing levobupivacaine plasma concentrations following caudal or spinal anaesthesia [2,3,7,8]. The cohort involved 110 patients [PMA 43.9 (37-49) weeks., PNA 6.52 months (0.6-32), weight 7.06 (1.96-15.5) kg] and 437 observations

2.4.2. ***Population parameter estimations***

A one-compartment linear disposition model with first order absorption and first order elimination was used to analyse time-concentration profiles. The model was parameterized in terms of clearance (CL), volume volumes of distribution (V) and an absorption rate constant (ka). The latter was expressed as an absorption half-life ($Tabs_{1/2}$).

Population parameter estimates were obtained using a non-linear mixed effects model (NONMEM VII, Globomax LLC, Hanover, MD, USA). The population mean parameters, between subject variance and residual variance were estimated using the first order conditional estimation method using ADVAN 2 TRANS 2[9]. Convergence criterion was 3 significant digits.

The population parameter variability is modelled in terms of random effect (η) variables. Each of these variables is assumed to have mean 0 and a variance denoted by ω^2, which is estimated. The population parameter variability in model parameters was modelled with an exponential model. We report the estimate of ω for each variability component expressed as a percentage because these quantities are approximate coefficients of variation for a log normal distribution. Residual unidentified variability was described using a combined proportional and additive residual error model for each observation prediction (Err_{PROP}, Err_{ADD})

2.4.3. Covariate analysis

The parameter values were estimated standardized for a body weight of 70 kg using an allometric model.[8]

$$Pi = P_{STD}\, x\, \left({Wi}/{W_{STD}}\right)^{EXP}$$

where P_i is the parameter in the *i*th individual, *Wi* is the weight in the *i*th individual and P_{STD} is the parameter in an individual with a weight W_{STD} of 70 kg. This standardization allows comparison of pediatric parameter estimates with those reported for adults. The *EXP* exponent was 0.75 for clearance and 1 for distribution volumes

Covariate analysis included a maturation model investigating age-related changes for clearance[3-5]

$$\text{CL} = CL_{STD}\, x\, \frac{PMA^{HILL}}{TM_{50}^{HILL} + PMA^{HILL}} \quad \frac{l}{h}$$

where CL_{STD} are the population estimates for CL, standardised to a 70 kg person using allometric models; PMA is the postmenstrual age in weeks; TM_{50} is the maturation half-time, and the Hill exponent relates to the steepness of the maturation profile.

2.4.4. Quality of fit

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 *versus* predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at α=0.05.

Bootstrap methods, incorporated within the Wings for NONMEM program, provided a means to evaluate parameter uncertainty. A total of 100 replications were used to estimate parameter confidence intervals. A visual predictive check (VPC), a modelling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations.

2.4.5.Simulation

A simulation study was performed to investigate plasma concentrations in neonates, infants and older children receiving a repeat caudal levobupivacaine at three or four hours after the initial

dose. Pharmacokinetic parameter estimates and their variability from this current analysis were used to predict individual time-concentration profiles.

3.Results:

3.1. Pharmacokinetic analysis

There were 80 plasma concentrations available for analysis from 21 infants [mean PMA of 59.0 (SD 5.9, range 49-70) weeks, mean PNA 21 (11-32) weeks and weight 6.9 (5.2-8.6) kg]. Repeat caudal anaesthesia at the end of surgery with 1 $mL.kg^{-1}$ of 0.25% levobupivacaine occurred on average (range) at 3.67 (3-5) hours after the first caudal and produced mean (range) C_{max} of 1.18 (0.51-2.35) $mg.L^{-1}$ and Tmax of 40.1 (4.8-124) min. Demographic data are shown in Table 1. These data were pooled with those from previous reports of levobupivacaine caudal and spinal anaesthesia. The pooled data involved 367 observations in 131 patients with a mean age 6.4 (range 0.6 – 32) months, PMA 43.9 (37-49) weeks. and mean weight 7.0 (1.96-15.5) kg.

Parameter estimates for the one-compartment linear disposition model are shown in **Table 2**. The final model incorporated allometric scaling of CL and V with the changes in CL due to postmenstrual age accounted for with a maturation function. Clearance changes with age are shown in **Figure 1. Figure 2** shows satisfactory PC-VPC plots for these pharmacokinetic data. **Figure 3** demonstrates the performance of the model with the data observed in the current study. This figure shows that observations from the current study were consistent with those predicted by the model using pooled data.

3.2. Simulation of clinical scenarios

Time-concentration profiles (**Figure 4)** simulated from a levobupivacaine pharmacokinetic model for a neonate (3.8 kg, 40 weeks PMA), an infant (7 kg, 57 weeks PMA) and a child (6 years, 20 kg) where an initial caudal levobupivacaine 2.5 mg.kg-1 is repeated at 4 hours. A mean peak total

concentration of 1.46 mg.L^{-1} was reached at 3.5 (3.2-4.2) h for the neonate, 1.46 mg.L^{-1} at 3.5 (3.2-4.2) h for the infant and 1.34 mg/L (0.57-2.53) at 4.53 h for the older child.

Simulations were performed using 1000 virtual infants from the same cohort as the study group (PNA 5-18 weeks, Gestation 21-41 weeks, weight 2.4-6 kg). Peak concentrations and the 97.5th centile for the prediction after repeat caudal are shown in **Table 3.**

4. Discussion

A repeat caudal dosing schedules of levobupivacaine (2.5 mg.kg^{-1} levobupivacaine repeated at 3 h) produces total drug concentrations less than 2.5 mg.L^{-1}, which is considered the lower limit of concentrations associated with local anaesthetic toxicity[10,11]. We have described levobupivacaine pharmacokinetics using major covariates of size (allometry) and maturation (postmenstrual age). These PK parameters and covariate influences were used to simulated scenarios to guide dosing schedules for repeated caudal blocks. These supported a decrease in dose of levobupivacaine to 1.25mg.kg-1 of 0.125% in neonates and delaying repeat caudal to more than 4 hours between blocks due to immature metabolic clearance.

A one-compartment linear disposition model with first order absorption and first order elimination was adequate to describe time-concentration profiles. This same structural model has been previously used to describe spinal and caudal blockades in neonates and infants[12]. In agreement with previous findings systemic absorption of levobupivacaine after caudal administration was relatively fast with an estimated absorption half-time ($Tabs_{1/2}$) of 6 min. The incorporation of PMA to describe metabolic clearance maturation provides a more physiologically appropriate description of clearance changes than previous models using PNA, since maturation of clearance begins in utero[13,14]. Levobupivacaine used for caudal anaesthesia in children less than 18 years of age has a reported elimination half-life of 14 hours in neonates and 3.6 hours in infants 6-18 months[15]. It has also been reported that clearance of levobupivacaine is only one-third of that in adults at 1 month of age, and two-thirds at 6 months postnatal age [4].

Our current model predicts the maturation of clearance reaches 50% at 50 weeks PMA and 77% at 60 weeks PMA. Adult values of clearances standardized to 70 kg using allometric relationships should be expected to occur by the end of the first year of life. (Figure 3).

Prospective paediatric regional anaesthesia studies have reported an overall incidence of local anaesthetic systemic toxicity (LAST) of 0.76 per 10,000 blocks but highlight the risk of LAST in children under 6 months old where LAST occurred seven times more frequently than other age groups[16,17] . Plasma concentrations of bupivacaine ,ropivacaine or levobupivacaine associated with LAST in children are rarely reported [10]. In adults the levobupivacaine plasma concentration for LAST is uncertain but has been described at concentrations as low as 2.62 mg. L^{-1}.[18,19] In children a conservative lower limit of 2.5 $mg.L^{-1}$ has been suggested [10]. No studies have reported plasma levobupivacaine concentrations during episodes of LAST in children [20]. In the current study only one patient reached a concentration that exceeded the concentration mooted to be associated with toxicity (2.5 $mg.L^{-1}$). In this patient a total concentration of 3.7 $mg.L^{-1}$ was measured. This occurred 30 minutes after the first caudal block and likely represents intravascular injection. No clinical complications or LAST symptoms were observed in this infant, possibly due to coadministration of general anaesthesia at the time of the high concentrations.

Only one prior study has reported repeated caudal local anaesthetic boluses in children. In a study of bupivacaine caudal anaesthetics in children 1-7 years old an initial caudal bolus of 0.75 $mL.kg^{-1}$ of 0.25% bupivacaine was performed followed by a second caudal with 0.375 $mL.kg^{-1}$ of 0.25% bupivacaine at a mean interval of 110 min[21]. The measured total bupivacaine Cmax was 0.71 (0.4-1.09) $mg.L^{-1}$and Tmax 21.9 min with no episodes of LAST. In the current study repeat caudal anaesthesia at the end surgery, with 1 $mL.kg^{-1}$ of 0.25% levobupivacaine occurred at mean (range) of 3.67 (3-5) hours after the first caudal block and produced mean (range) Cmax and Tmax of 1.18 (0.51-2.35) mg.L-1and 40.1 (4.8- 124) min, respectively, which can be considered within an acceptable margin of safety when related to currently used toxic thresholds. Although

both studies support their dose schedules, it is difficult to compare results because of differences in the drug used, the dosing schedules and intervals between caudal blocks.

According to our final model predictions mean Cmax and Tmax of 1.38 mg.L^{-1} (95% CI 0.58, 2.6) and 4.5 h (95% CI 4.2-5.2) should be expected in typical patients of 7 kg, 57 weeks PMA after repeated caudal blocks separated by 4 hours with 2.5 mg. kg^{-1} of 0.25% levobupivacaine. This same per kilo dose, however, given in neonates of 3.8 kg, 40 weeks PMA will produce much higher Cmax and Tmax of 1.76 mg.L^{-1} (95% CI 0.68-3.47) and 4.7 h (95% CI 4.3-5.7), respectively (Table 3). Immature clearance in neonates explain the relatively higher Cmax and longer Tmax predicted in this population and posed them at more risk of reaching toxic thresholds [2,22,23]. Whilst the risk of total concentrations broaching the lower concentration associated with LAST is low in infants and older children caution is advised for neonates. It would appear prudent to reduce total dose when repeat caudal anaesthesia is required in neonates.

One limitation of this study is the inability to measure and report unbound levobupivacaine concentrations. We report total plasma concentrations that are reflective of *alpha-1-acid* glycoprotein (AAG) concentrations. This reactive protein concentration increases over the first year of life and also increases after surgical insult. However, there is limited variability with AAG concentrations in the cohort investigated and changes after surgery are small in the limited duration of this current study [24-26]. The unbound plasma concentration identified as the concentrations associated with systemic toxicity in children has not been described. There are also possibly other mitigating factors influencing observed toxic effects such as rate of rise of plasma concentrations. In addition pharmacodynamics factors such as the concomitant use of general anaesthesia during caudal anaesthesia and the increased sensitivity of the neonatal myocardium to local anaesthetics all impact on the expression of systemic toxicity.

Disclosures:

Conflict of Interest: Brian Anderson is a section editor for the journal, Pediatric Anesthesia.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Clinical Trials Registration: not applicable

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Tables

Table 1. Demographics of infants undergoing definitive repair of anorectal malformations or Hirschsprung's disease who received an initial caudal anaesthetic of 2.5 $mg.kg^{-1}$ levobupivacaine followed by a second caudal of 2.5 $mg.kg^{-1}$ levobupivacaine at the end of the procedure (3-4 hours) Values are presented as mean (SD).

		Repeat caudal at 3 hours n=11	Repeat caudal at 4 hours n=10
Gender	Male (%)	9 (82%)	9 (90%)
Gestational Age	weeks	38.1(0.7)	39.1 (0.9)
Birth weight	kg	3.21 (0.43)	3.36 (0.45)
Post Menstrual age	months	4.98 (1.8)	5.10 (1.1)
Current weight	kg	6.55 (0.85)	7.46 (0.9)
Surgery	Anorectal anomaly (%) Hirschsprung's (%)	10 (91%) 1 (9%)	3 (30%) 7 (70%)
Surgical Time	minutes	142.4 (24.8)	202.7 (29.2)
Anaesthetic Time	minutes	184.1 (27.4)	243 (26.9)

Table 2. Standardised levobupivacaine population pharmacokinetic parameter estimates (Vstd and CLstd are the population estimates for volume and clearance, respectively, standardized to a 70 kg person using allometric theory; Tabs and TM_{50} (weeks PMA) are the absorption half-times and maturation half-time of clearance, BSV is the between subject parameter variability, SE is the standard error of the estimate, CI is the confidence interval)

Parameter		**Estimate**	**%BSV**	**%SE**	**95% CI**
CLstd (L/h/70kg)		21.7	49.3	16.1	16.2, 29.2
Vstd (L/70kg)		194	49.8	5.1	179, 209
$Tabs_{1/2}$ (Spinal) h		0.4		21.1	0.02, 0.06
$Tabs_{1/2}$ (Caudal h)		0.1	54.1	8.7	0.08, 0.12
TM_{50} (weeks PMA)		50.1	-	6.8	46.0, 85.5
Hill		6.8	-	70.8	1.06, 111,6
Residual Error	Additive (mg/L)	0.0467	-	11.1	0.0204, 0.0544
	Proportional (%)	16.6	-	25.2	11.7, 18.9

Table 3. Peak total levobupivacaine concentrations after repeat caudal at either 3 or 4 hours and their 97.5% CI in neonates, infants and children. For simulation a standard neonate was defined as 3.8kg, PMA 40 wks., an infant as 7kg,57 weeks PMA and a child as 6 yrs., 20kg. Cmax, Maximum concentration observed; Tmax, Time of Maximum concentration observed.

Patients	Time between caudals	Initial Caudal dose	Repeat caudal dose	Cmax (95%CI) $mg.L^{-1}$	T max (95%CI) hrs.
Neonates < 6 weeks	4 h	2.5 $mg.kg^{-1}$	2.5 $mg.kg^{-1}$	1.76 (0.68, 3.47)	4.7 (4.3, 5.7)
	4 h	1.25 $mg.kg^{-1}$	1.25 $mg.kg^{-1}$	0.88 (0.34, 1.73)	4.7 (4.3, 5.7)
	6 h	2.5 $mg.kg^{-1}$	1.25 $mg.kg^{-1}$	1.07 (0.77, 1.29)	6.4 (6.3, 6.8)
	6 h	2.5 $mg.kg^{-1}$	2.5 $mg.kg^{-1}$	1.44 (1.10, 1.80)	6.5 (6.4, 6.7)
Infants 4-7 months	3 h	2.5 $mg.kg^{-1}$	2.5 $mg.kg^{-1}$	1.46 (0.60, 2.80)	3.5 (3.2, 4.2)
	3 h	2.5 $mg.kg^{-1}$	1.25 $mg.kg^{-1}$	1.04 (0.43, 1.95)	2.8 (0.3, 4.1)
	4 h	2.5 $mg.kg^{-1}$	2.5 $mg.kg^{-1}$	1.38 (0.6, 2.6)	4.5 (4.2, 5.2)
Children 6 years	3 h	2.5 $mg.kg^{-1}$	2.5 $mg.kg^{-1}$	1.43 (0.59, 2.72)	3.53 (3.2, 4.2)
	4 h	2.5 $mg.kg^{-1}$	2.5 $mg.kg^{-1}$	1.34 (0.57, 2.53)	4.53 (4.2, 5.2)

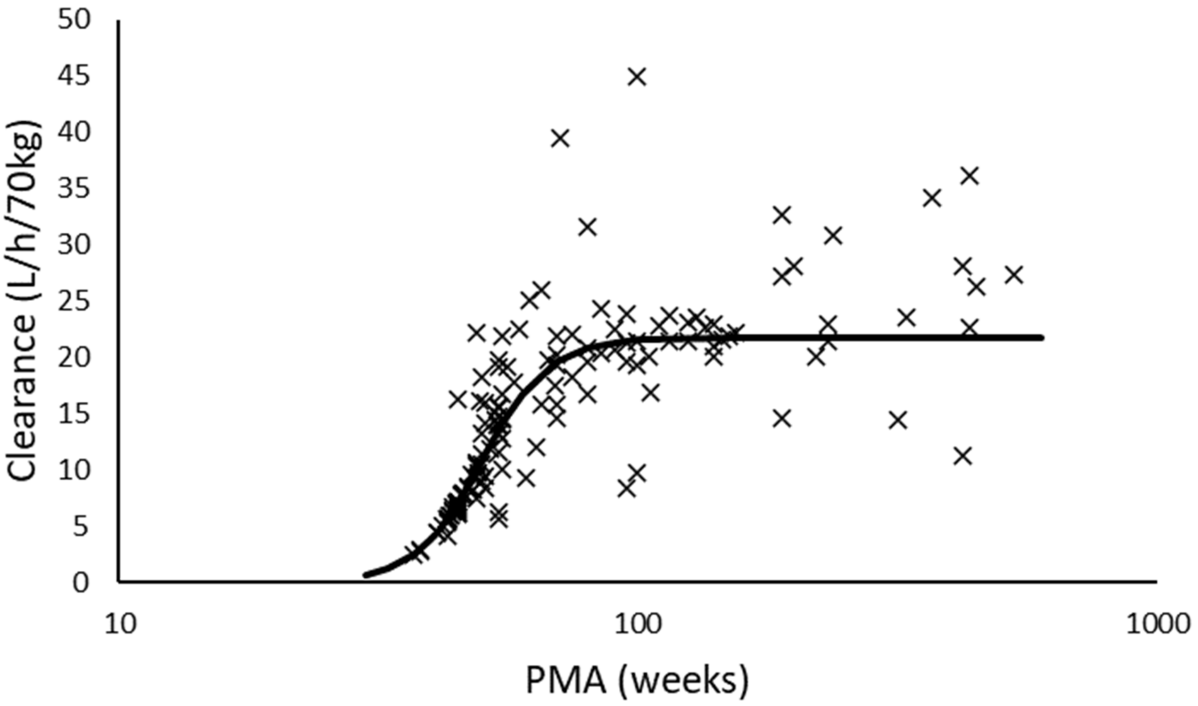
Figures Legends

Figure 1. Maturation of levobupivacaine clearance using pooled data. The mean population fit is described by the solid line. Individual bayesian clearance estimates are shown as crosses

Figure 2 Visual predictive check for the levobupivacaine PK model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all prediction corrected observed concentrations. Right hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (grey shaded areas).

Figure 3. Prediction-corrected visual predictive check (PC-VPC) for the levobupivacaine data obtained only in current study using the pooled pharmacokinetic model predictions. Plots show median (solid) and 90% intervals (dashed lines). The left-hand plot shows all prediction corrected observed levobupivacaine concentrations. Right hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (grey dashed lines) and predictions (red dashed lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5th and 95th blue shading).

Figure 4. Time-concentration profile simulated from a levobupivacaine pharmacokinetic model for a neonate (3.8 kg, 40 weeks PMA), an infant (7 kg, 57 weeks PMA) and a child (6 years, 20 kg) where an initial caudal levobupivacaine 2.5 $mg.kg^{-1}$ is repeated at 4 hours. A mean peak total concentration of 1.46 $mg.L^{-1}$ was reached at 3.5 (95% CI 3.2-4.2) h for the neonate, 1.46 $mg.L^{-1}$ at 3.5 (3.2-4.2) h for the infant and 1.34 $mg.L^{-1}$ (0.57-2.53) at 4.53 h for the older child. In neonates the 97.5% confidence interval for total plasma concentration broaches the line representing the lower limit of concentrations associated with local anaesthetic toxicity (2.5 $mg.L^{-1}$).



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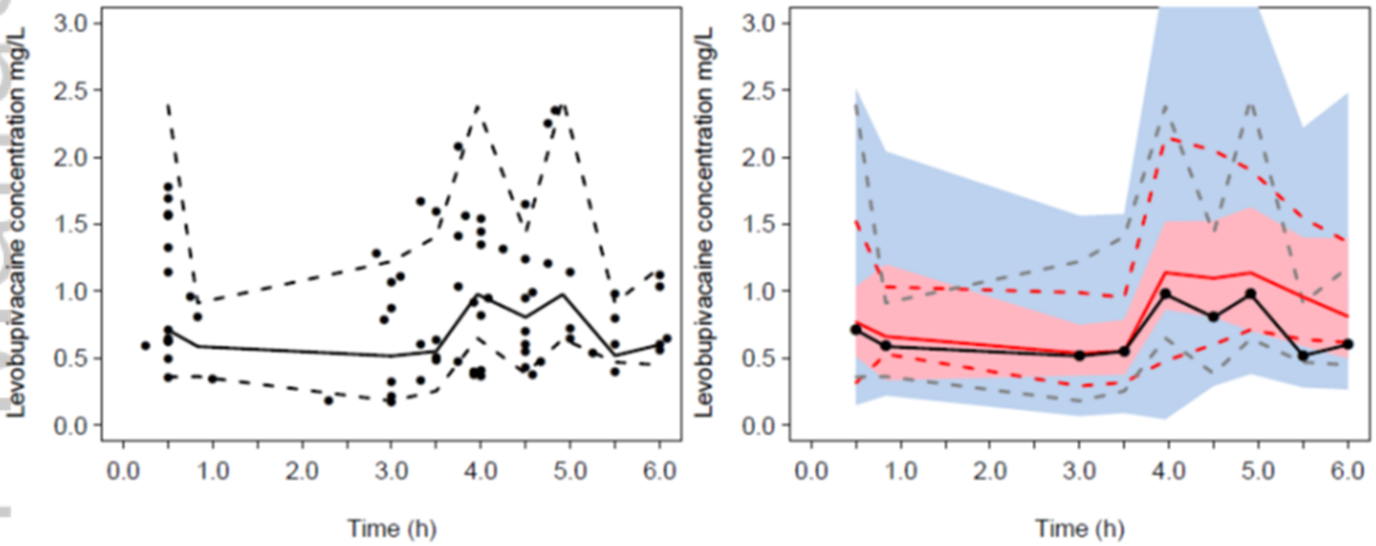

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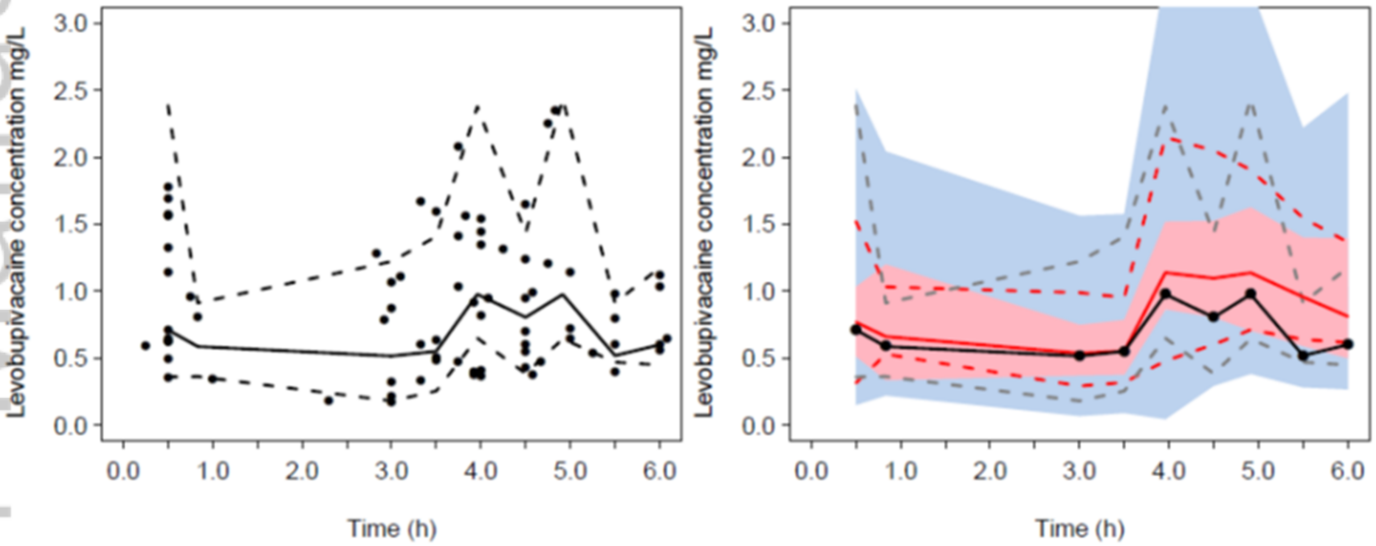

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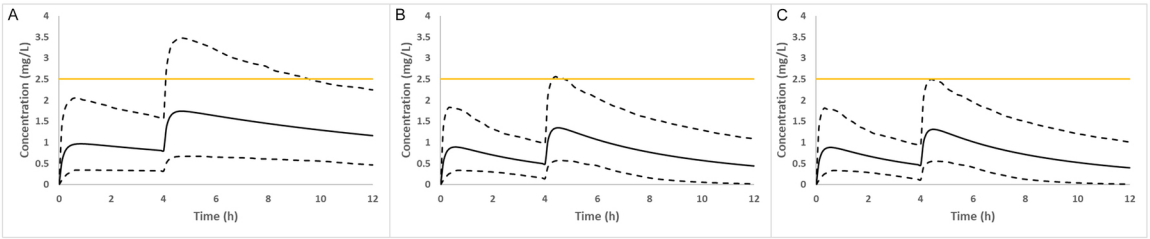

PAN_14556_Figure 4 Simulations.jpg