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Abstract

Background

Infant spinal anaesthesia with levobupivacaine has been promoted as a technique to reduce both the risk of postoperative apnoea and exposure to volatile anaesthesia. There is however no pharmacokinetic data to support the currently recommended doses.

Aims

Our aim was to determine whether infant levobupivacaine spinal anaesthesia is associated with plasma concentrations consistent with a low risk of local anaesthetic systemic toxicity.

Methods

This was an open label pharmacokinetic safety and tolerability study of levobupivacaine spinal anaesthesia in infants less than 55 weeks PMA undergoing lower abdominal surgery. Infants received a spinal anaesthetic with levobupivacaine 1 mg.kg⁻¹ in the left lateral position.

Results

Spinal anaesthesia was successful in 25 (86.2%) of twenty nine infants (postmenstrual age 36-52 wks; weight 2.2-4.7 kg). The median (IQR) total venous levobupivacaine plasma concentrations was 0.33(0.25-0.42) ug.mL⁻¹ and unbound venous levobupivacaine 19.5 (14.5-38) ng.mL⁻¹. Median protein binding was 93.5 (91.4-96%). Alpha-1 acid glycoprotein concentrations were 0.25(0.17-0.37) g/l and albumin concentrations 29 (24-32) g.L⁻¹.

Conclusion

Total plasma concentrations and unbound (free) concentration of levo-bupivacaine were consistently lower than concentrations reported in cases of paediatric local anaesthetic toxicity. In a small number of infants requiring a repeat spinal of 1 mg.kg⁻¹ was also associated with acceptable total and free concentrations. We conclude that levo-bupivacaine at 1 mg.kg⁻¹ is associated with no systemic side effects in infants receiving awake spinal anaesthesia.

Key words: Anesthesia, spinal; Anesthetics, local; Levobupivacaine; Infant; Protein binding; Orosomucoid.

Clinical implications:

What is already known about the topic?

Immature neonatal metabolic pathways impact on local anaesthetic metabolism and put infants at risk of local anaesthetic systemic toxicity at doses considered safe in older children. Decreased alpha 1 acid glycoprotein concentrations in neonates results in higher unbound local anaesthetic concentrations and potentially increased risk of local anaesthetic toxicity.

What new information this study adds:

Levobupivacaine when used for infant spinal anaesthesia is associated with total and unbound concentrations which are unlikely to induce systemic toxicity.

Background and Significance

The pharmacokinetics of local anaesthetics in neonates have been poorly quantified but it is known that differences in physiology, enzyme maturation and clearance mechanisms vary widely between adults and infants and will impact on drug handling (1). Neonates have reduced concentrations of albumin and α -1-acid glycoprotein and therefore reduced protein binding and higher unbound (free) levobupivacaine concentrations. Preterm infants have even lower concentrations of α -1-acid glycoprotein than term infants making them particularly susceptible to local anaesthetic systemic toxicity (LAST). Neonates and young infants have delayed maturation of hepatic cytochrome P450 (CYP3A4 for levobupivacaine) resulting in a prolonged elimination half-life of amide local anesthetics. The hepatic conjugation oxidation system in infants does not mature to adult functional levels until approximately 6 months of age (2, 3). In addition to decreased clearance of amide local anesthetics, infants have a greater volume of distribution, an increased elimination half-life, and decreased clearance compared with older children(4).

The clinical implication of the highly variable physiology of preterm infants and their different responses to local anaesthetics by stage of gestation is that higher free concentrations of local anaesthetics are common and dose modification may be necessary. Pharmacokinetic studies of a single dose of caudal racemic bupivacaine (2.5 mg.kg^{-1}) have demonstrated differences between infants and children and recommended lower doses in infants less than three months of age (). There are however few pharmacokinetic studies to guide dose selection for spinal anaesthesia in neonates. Most recommended spinal anaesthetic doses are empiric weight based formulas which are not supported by pharmacokinetic studies (1, 8).

Aim: The main objective of this study was to evaluate blood levobupivacaine concentrations in neonates after spinal anaesthesia. We hypothesised that spinal blocks would not result in unacceptably high local anaesthetic concentrations when performed in neonates. We also specifically sought to estimate the 99% upper prediction limit of blood levobupivacaine concentrations across multiple time points across 90 minutes after the local anaesthetic injection.

Methods

The Royal Children's Hospital Ethics Committee granted approval for this study (HREC 33045A). Infants less than 55 weeks post menstrual age and scheduled to undergo sub-umbilical surgery were identified from the Royal Children's Hospital theatre booking system. Reporting of the study was performed according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) consensus (9). After agreement from the treating anesthetist, informed consent was obtained from a parent or legal guardian for their child to participate in the study. Exclusion criteria included any contraindication to spinal injection including bleeding disorders in

the child or their family, allergy, or previous adverse response to racemic bupivacaine or levobupivacaine. From June 2013 we enrolled 25 infants undergoing elective sub-umbilical surgical procedures for which spinal anaesthesia was indicated. Patients received 1 mg.kg^{-1} of 0.5% levobupivacaine.

Venous peripheral blood samples were collected from an indwelling catheter not in use for drug and/or fluid infusion. After each sample the i.v. cannula was flushed with 1 ml of heparinized saline ($10 \text{ u heparin.mL}^{-1}$). A maximum of 4 samples were collected within the clinically determined spinal anaesthetic phase up to 80 minute from the spinal dose. The sample collection times for each patient were determined according to a randomised schedule over the dose interval to ensure an even distribution of plasma samples across the clinical anaesthesia phase.

Patients were awake during surgery and monitored for the presence of signs of central nervous system local anaesthetic toxicity including sensory disturbance, muscle twitching or seizures, Continuous monitoring of blood pressure and electrocardiographs during surgery and the postoperative care unit was used to detect cardiac systemic toxicity.

Plasma levobupivacaine assay:

Blood samples were processed within 1 h of collection. Each sample was centrifuged and then stored in a cryotube at -80°C pending batched plasma levobupivacaine assay. The plasma levobupivacaine assays were conducted in 3 batches, one for each study group.

Plasma concentrations of levobupivacaine were determined by capillary gas chromatography on a Shimadzu GC-17A (Kyoto, Japan). An internal standard (mepivacaine) was added to 0.2 ml of plasma in a borosilicate tube. Saturated potassium hydroxide, KOH solution (0.025 ml) was added, and the samples mixed before adding 4 ml of ethyl acetate. The borosilicate tubes were capped, vortexed for 10 s , and centrifuged at 1300 g for 5 min . The upper organic layer was transferred into a second borosilicate tube and evaporated to dryness under nitrogen at 100°C . The residue was reconstituted in 0.1 ml of methanol with $0.025 \mu\text{l}$ of the sample to be injected into the gas chromatograph. The chromatograph used a programmable temperature vaporizer, a $30 \times 0.25 \text{ mm BPX50}$ column (SGE), and nitrogen–phosphorous detection. The method is linear to at least 2000 ng.mL^{-1} , with a limit of quantification of 0.05 mg.L^{-1} and a coefficient of variation of 4.4% at 0.2 mg.L^{-1} . Unbound levobupivacaine concentrations were determined after ultrafiltration.

Quantification of human AAG in patient plasma

Patient blood was centrifuged for 15 min at $1000 \times \text{g}$ and aliquots of the plasma samples were stored at -80°C . In accordance with the manufacturer's instructions (Human alpha 1-Acid Glycoprotein Quantikine ELISA Kit, Minneapolis, U.S.A) plasma was diluted to 1:10,000 using the given calibrator diluent RD5-20. The assay mixture per well in the provided 96-well plate contained $100 \mu\text{L}$ assay diluent RD1-73 and $50 \mu\text{L}$ standard or the diluted patient plasma. The plate was then covered with an adhesive strip and incubated for 2 h at 25°C . The optical density

of each well was then measured using a microplate reader set to 450 nm. The concentration of AAG present in the patient samples was determined from a standard curve generated using known concentrations of purified human AAG provided by the manufacturer.

Statistics

As the primary aim was to determine the plasma concentration profile of levobupivacaine no power calculation was performed. No formal sample size calculation was performed but a sample of 25 infants was considered to provide sufficient information on the plasma concentration profile of levobupivacaine. This sample size was consistent with comparable infant pharmacokinetic studies (10, 11) and has the power to detect a 20% difference in the peak concentration of levobupivacaine with $\alpha=0.05$ and $\beta=0.8$.

Baseline characteristics and clinical outcomes for all infants were analysed using t tests, Fishers exact tests, ANOVA or Kruskal-Wallis tests as appropriate. Mean and standard deviation (SD) of the total and unbound plasma levobupivacaine concentrations at each time-point were calculated. The Kolmogorov-Smirnov test for normality was used for the values from each subject at 30 minutes to confirm that the data followed a normal distribution. The 99% upper prediction limit intervals for the plasma bupivacaine concentrations across subsequent times were calculated. We used linear mixed effects modeling adjusting concentration for the fixed effects of current weight and dose and the random effects of gestational age, post menstrual age and AAG concentration.

Results

Spinal anesthesia alone was attempted in 29 patients and was sufficient for the completion of surgery in 25 patients (86.2%). Four infants demonstrated no significant motor block after the first spinal dose despite adequate CSF flow on initial lumbar puncture. In these infants a second dose of levobupivacaine 1 mg.kg^{-1} was used and was clinically effective. The demographics of the analyzed patients are presented in table 1. Compared to the successful spinal group there was no significant difference in the weight ($p=0.58$) or PMA ($p=0.96$) of the infants in whom the first spinal failed.

Individual patient's plasma levobupivacaine concentrations are plotted against time (Fig. 1). The median peak venous total plasma concentrations (C_{max}) of levobupivacaine were $0.34 \text{ } \mu\text{g.mL}^{-1}$ (interquartile range [IQR], $0.27\text{--}0.38 \text{ } \mu\text{g.mL}^{-1}$). The median peak venous unbound plasma concentrations (CU_{max}) of levobupivacaine were $0.02 \text{ } \mu\text{g.mL}^{-1}$ (IQR $0.01\text{--}0.04 \text{ } \mu\text{g.mL}^{-1}$). The median times to maximum plasma levobupivacaine concentration (T_{max}) were 30 (IQR, 25–40) min. In those infants who received a second spinal anaesthetic the mean C_{max} was $0.588 \text{ } \mu\text{g.mL}^{-1}$ (IQR, $0.465\text{--}0.773 \text{ } \mu\text{g.mL}^{-1}$), mean unbound plasma concentrations (CU_{max}) was $0.036 (16.1) \text{ } \mu\text{g.mL}^{-1}$ and the mean T_{max} was 45 (IQR 27–60) min. Plasma concentrations are reported in Table 2. The 99% upper prediction limit intervals for the plasma levobupivacaine concentrations were calculated at 5,10,15,20,25,30,35,40 and 50 minutes at which times 8,7,7,5,9,9,8,5 and 3

samples respectively had been collected. None of the 99% upper prediction limit intervals for the plasma levobupivacaine concentrations crossed potentially toxic levobupivacaine concentrations at any time after injection.

As expected the alpha 1 acid glycoprotein (AAG) concentrations were low and the unbound concentration higher than older children. The median AAG concentrations were 0.25 (0.17-0.37) mg.mL⁻¹. There was no association between AAG concentrations and gestational age (p=0.23), post menstrual age (p=0.98) or current weight (p=0.63) using linear regression. The median unbound fraction was 7.24% (IQR 4-10.1%).

Linear mixed effect modeling of the dose response data adjusting concentration for gestational age, post menstrual age, dose and current weight demonstrated significant correlation with PMA alone (p= 0.01). It was not possible to use NONMEM pharmacokinetic modeling on this sample to determine the exact C_{max} and T_{max}. Future studies would need to extend the sampling period to greater than the 70 minutes of this study to accurately describe the elimination phase of spinal levobupivacaine.

There were no episodes in any of the patients of symptoms or signs suggestive of either CNS or CVS toxicity as noted by either the postoperative care unit nurses or the authors who were present throughout the study period.

Discussion:

In this study both the total and free levobupivacaine concentrations were lower than concentrations considered to be well tolerated by adults (2-4 µg.mL⁻¹ and 0.11-0.3 µg.mL⁻¹ respectively). The highest individual total levobupivacaine concentrations (0.68 µg/l after a single dose or 0.861 after two doses) were not associated with any clinical signs of toxicity. The toxicity of levobupivacaine is more likely to be related to the free plasma concentrations (C_{u, max}) rather than the total plasma concentration. In our study, the mean free C_{u, max} was 27.9(19.1) µg/l and the mean percentage of free levobupivacaine was 7.6% (sd 3.5%). Unbound bupivacaine concentration in excess of 34 pg.mL⁻¹ (albeit measured at 5-8 hours of epidural infusion) have been reported to cause early systemic toxicity (jitteriness)(). In contrast unbound bupivacaine concentrations after single caudal anaesthesia of 50 pg.mL⁻¹ did not produce clinical toxicity(13). An unbound levobupivacaine concentration in excess of 35 pg.mL⁻¹ occurred in 8 (27%) of infants in the current study without overt clinical toxicity which may indicate a greater safety margin for levobupivacaine. Reassuringly the use of second spinal anaesthetic (total dose 2mg.kg⁻¹) did not produce plasma total and free concentrations associated with an increased risk of toxicity.

There are few studies describing pharmacokinetic aspects of infant spinal anaesthesia in the literature and none describing levobupivacaine (). Beauvoir measured total and free bupivacaine after spinal anaesthesia in twenty-two newborns with a single blood sample collected ten min after spinal injection. Total bupivacaine concentration [mean (sd)] was found to be 0.31

(0.17) $\mu\text{g}\cdot\text{mL}^{-1}$ which is below the toxic threshold but protein binding was only 87%. Frawley reported the unbound and bound plasma concentration of bupivacaine in 50 infants less than 55 weeks post conceptual age following combined spinal and epidural anaesthesia (CSEA) (). Total plasma concentrations above a toxic threshold level of $4\ \mu\text{g}\cdot\text{mL}^{-1}$ were recorded in 4% of patients and above $2.5\ \mu\text{g}\cdot\text{mL}^{-1}$ in 10% of patients. Unbound bupivacaine concentrations were greater than a presumed toxic level of $0.25\ \mu\text{g}\cdot\text{mL}^{-1}$ in 16% of cases. In both studies variable local anaesthetic binding occurred due to reduced albumin and highly variable alpha-1 acid glycoprotein (AAG) concentrations (0.11-0.95 g/l) ().

Two recent pharmacokinetic studies of levobupivacaine infusions in neonates suggest that elevated plasma total concentrations can occur even with conservative doses and concentrations. Anell-Olofsson reported plasma concentrations of levobupivacaine in the first 24 hours of 0.0625% levobupivacaine wound infusion post neonatal thoracotomy. The median total levobupivacaine concentrations was $0.55\ \mu\text{g}\cdot\text{mL}^{-1}$ if infusion of levobupivacaine started 8 hours postoperatively and $1.68\ \mu\text{g}\cdot\text{mL}^{-1}$ following a $0.2\text{mg}\cdot\text{kg}^{-1}$ bolus and $2\text{mg}\cdot\text{kg}\cdot\text{day}^{-1}$ infusion (18). Krylborn reported unbound levobupivacaine plasma concentrations were stable and below $0.05\ \mu\text{g}\cdot\text{mL}^{-1}$ up to 72 hours postoperatively using wound catheter infusions (19). A significantly higher maximum plasma concentration (C_{max}) in infants less than three months compared to older children has also been reported after single shot caudal techniques involving racemic bupivacaine (10, 20).

Toxicity:

The reported incidence of LAST in infants and children is low (21-24), is largely the result of continuous bupivacaine lumbar or caudal epidural anesthesia and has never been reported after spinal anaesthesia (25, 26). Adult volunteer studies suggest the CNS toxicity threshold of venous total bupivacaine concentration of $2.1\ \mu\text{g}\cdot\text{mL}^{-1}$ and unbound bupivacaine concentration of $0.11\ \mu\text{g}\cdot\text{mL}^{-1}$ (27). Concentrations leading to systemic toxicity in children are largely unknown but have been presumed to occur at plasma total concentrations greater than $2\ \mu\text{g}\cdot\text{mL}^{-1}$ (7, 12, 28, 29). In practice however systemic toxicity in children occurs at a wide range of concentrations (Table 3) (12, 26, 30-34). McCloskey reported a neonate sustained bradycardia and hypotension, and two older children with seizures following continuous caudal infusions of 0.25% bupivacaine at 1.67 to $2.5\ \text{mg}\cdot\text{kg}^{-1}$ per hour. Bupivacaine serum concentrations at the time of the event ranged between 5.6 and $20.3\ \mu\text{g}\cdot\text{mL}^{-1}$. Agarwal reported two children who developed racemic bupivacaine induced seizures. In one child the seizure occurred with a plasma bupivacaine level of $5.6\ \mu\text{g}\cdot\text{mL}^{-1}$ following intrapleural catheter infusion at $0.5\ \text{mg}\cdot\text{kg}\cdot\text{hr}^{-1}$ whereas in the other child seizures occurred with a plasma bupivacaine level of $5.4\ \mu\text{g}\cdot\text{mL}^{-1}$ following continuous epidural infusion of $1.25\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$. This would suggest a paediatric total bupivacaine LAST threshold of $4\ \mu\text{g}\cdot\text{mL}^{-1}$. Other studies have reported higher plasma concentrations of bupivacaine (1 to $7\ \mu\text{g}\cdot\text{mL}^{-1}$) without clinical evidence of toxicity but benzodiazepines may have masked signs of LAST (35).

Limitations:

We measured venous levobupivacaine drug concentrations in the current study and these may well be somewhat lower than those in arterial blood (27, 36). Without a priori knowledge of the elimination phase of infant spinal anaesthesia an assumption was made that the phase duration would mirror the duration of clinical anaesthesia (typically 70 minutes after the block onset). Unfortunately there was no consistent decline in concentrations over the sampling time frame possibly due to reduced redistribution and metabolism. The limited data points in the late terminal elimination phase prevented estimation of clearance and V_D with any real reliability. Future studies should extend sampling past 70 minutes to capture the terminal elimination phase.

Conclusions:

Total plasma levobupivacaine concentrations were below accepted safe concentrations but protein binding by AAG and unbound concentrations were unpredictable and caution should be exercised in exceeding maximum doses used for infant spinal anaesthesia.

Disclosures:

Ethics; HREC 33045A RCH Human Research Ethics Committee, The Royal Children's Hospital 23rd April 2013

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Disclosures; The authors have no conflict of interest to declare.

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Caption

Figure 1. Box and whisker plot demonstrating total plasma levobupivacaine concentrations over time for individuals following spinal anaesthesia. The first and third quartiles are at the ends of the box, the median is indicated with a vertical line in the interior of the box, and the maximum and minimum are at the ends of the whiskers. Black horizontal lines denote the 99% upper prediction limit for plasma levobupivacaine across different times after spinal block.

Table 1. Demographics of infants receiving 1mg.kg^{-1} levobupivacaine spinal anaesthetics. In four cases inadequate motor block occurred despite CSF flow on initial dural puncture and received a second spinal anaesthetic of the same dose. Mean (standard deviation) are shown for continuous variables and n (%) for binary variables.

Table 2. Plasma concentrations following infant spinal anaesthesia with 1mg.kg^{-1} levobupivacaine. Four infants demonstrated no significant motor block after the first spinal dose despite adequate CSF flow on initial lumbar puncture. In these infants a second dose of levobupivacaine 1mg.kg^{-1} was used and was clinically effective. Plasma concentrations of total and unbound levobupivacaine were measured by capillary gas chromatography (HPLC) and Alpha 1-Acid Glycoprotein (AAG) by Enzyme-Linked Immunosorbent Assay (ELISA).

Table 3. Case reports of paediatric local anaesthetic systemic toxicity (LAST) where plasma concentrations have been recorded.

		Spinal n=25	2 Spinals n=4
Gender	Male (%)	23 (92%)	4 (100%)
Gestational age	Wks	34.2 (5.1)	35 (4.1)
Birth Wt	Kg	2.15 (0.83)	2.15 (0.83)
Post Menstrual age	Wks	43.8 (3.2)	43.7 (1.7)
Current Wt	Kg	4.19 (0.79)	3.94 (1.3)
Age at surgery	Wks	9.7 (3.9)	8.8 (1.5)
Surgery	Unilateral (%)	16 (64%)	2 (50%)
Surgical time	Unilateral	32.2 (3.2)	37.5 (2.7)
	Bilateral	41.8 (2.4)	40.5 (2.1)
Anaesthetic time	Unilateral	46.4 (3.9)	46.4 (3.9)
	Bilateral	53.02 (4.4)	53.0 (4.3)

Table 1. Demographics of infants receiving 1mg.kg⁻¹ levobupivacaine spinal anaesthetics. In four cases inadequate motor block occurred despite CSF flow on initial dural puncture and received a second spinal anaesthetic of the same dose. Mean (standard deviation) are shown for continuous variables and n (%) for binary variables.

		Median	IQR
Total plasma Levobupivacaine $\mu\text{g.ml}^{-1}$	One Spinal	0.33	0.25-0.42
	Repeat Spinal	0.58	0.47-0.77
Unbound Levobupivacaine ng.ml^{-1}	One Spinal	19.5	14.5-38
	Repeat Spinal	37	24-48
Unbound Fraction		6.5%	4-9.6%
Alpha 1 Acid Glycoprotein g.l^{-1}		0.25	0.17-0.37
Albumen g.l^{-1}		29	24-32

Table 2. Plasma concentrations following infant spinal anaesthesia with 1mg.kg^{-1} levobupivacaine. Four infants demonstrated no significant motor block after the first spinal dose despite adequate CSF flow on initial lumbar puncture. In these infants a second dose of levobupivacaine 1mg.kg^{-1} was used and was clinically effective. Plasma concentrations of total and unbound levobupivacaine were measured by capillary gas chromatography (HPLC) and Alpha 1 Acid Glycoprotein (AAG) by Enzyme-Linked Immunosorbent Assay (ELISA).

	Block	Ref	Agent and Dosage	Age of Child	C _T (µg.ml ⁻¹)	C _U (µg.ml ⁻¹)	Presentation
Single Block	Caudal	7	Bupiv	1-6mo	0.97		No events
			2.5mg.kg ⁻¹ Ad		(0.55-1.93)		
	Caudal	32	Bupivacaine	36-52wks	0.97		Abnormal EEG Jittery
			3.1mg.kg ⁻¹ Ad		(0.56-1.62)		
Continuous Infusion	Caudal	13	Bupivacaine 0.25%	10 mo-8yrs		Bupi 0.05	No events
			Ropivacaine			Ropi 0.06	
	Caudal	33	Ropivacaine	Preterm	6		Ventricular arrhythmia
			10mg.kg ⁻¹		1.2(8hrs)		
	Epidural	30	Bupivacaine	9yo	5.4		Seizure
			0.5 mg.kg ¹ .hr ⁻¹				
	Intra-pleural	30	Bupivacaine	3yo	5.6		Seizure
			0.1 mg.kg.hr ⁻¹				
	Caudal catheter	34	Bupivacaine	Term	5.6		Ventricular arrhythmia
			0.1 mg.kg.hr ⁻¹		3.7(12hr)		
			Bupivacaine	Term	Lost		Ventricular arrhythmia
			1ml.kg ⁻¹				
	Caudal	31	Bupivacaine	Term	5.6		Ventricular arrhythmia
	Epidural		2.5mg.kg.hr		3.7(12hr)		
			Bupivacaine	8yo	6.6		Seizure
			1.67 mg.kg.hr				

		Bupivacaine 1.67 mg.kg.hr ⁻¹	4yo	10.2		Seizure
Epidural	26	Bupivacaine 0.125%	1-2 yo	2.1-5.5		Jitteriness Convulsion
Thoracic Epidural	12	Bupivacaine 0.3 mg.kg.hr ⁻¹	6days-3mo	0.88 (0.46-1.47)	0.034 (0.02-0.07)	Jittery
Intra- pleural	35	Bupivacaine 1.25 mg.kg.hr ⁻¹		7.0		Asymptomatic

Table 3. Case reports of paediatric local anaesthetic systemic toxicity (LAST) where plasma concentrations have been recorded.

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