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Title:

Pharmacokinetics of levobupivacaine following infant spinal anesthesia

Date:

2016-06-01

Citation:

Frawley, G., Hallett, B., Velkov, T., Bjorksten, A. & Anderson, B. (2016). Pharmacokinetics of levobupivacaine following infant spinal anesthesia. *Paediatric Anaesthesia*, 26 (6), pp.575-581. <https://doi.org/10.1111/pan.12899>.

Persistent Link:

<https://hdl.handle.net/11343/291155>

Received Date : 30-Dec-2015

Revised Date : 08-Mar-2016

Accepted Date : 10-Mar-2016

Article type : Research Report

**Title:** Pharmacokinetics of levo-bupivacaine following infant spinal anaesthesia.

**Running head (Short title):** Infant Spinal Levo

**Article category:** Research report

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/pan.12899](https://doi.org/10.1111/pan.12899)

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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  $1 \text{ mg.kg}^{-1}$  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  $0.33(0.25-0.42) \text{ ug.mL}^{-1}$  and unbound venous levobupivacaine  $19.5 (14.5-38) \text{ ng.mL}^{-1}$ . Median protein binding was 93.5 (91.4-96%). Alpha-1 acid glycoprotein concentrations were  $0.25(0.17-0.37) \text{ g/l}$  and albumin concentrations  $29 (24-32) \text{ g.L}^{-1}$ .

### 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  $1 \text{ mg.kg}^{-1}$  was also associated with acceptable total and free concentrations. We conclude that levo-bupivacaine at  $1 \text{ mg.kg}^{-1}$  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  $\alpha$ -1-acid glycoprotein and therefore reduced protein binding and higher unbound (free) levobupivacaine concentrations. Preterm infants have even lower concentrations of  $\alpha$ -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 ( $2.5 \text{ mg.kg}^{-1}$ ) 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 anaesthetist, 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  $1 \text{ mg}\cdot\text{kg}^{-1}$  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 ( $10 \text{ u heparin}\cdot\text{mL}^{-1}$ ). 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  $-80^\circ\text{C}$  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  $100^\circ\text{C}$ . 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 mm BPX50 column (SGE), and nitrogen-phosphorous detection. The method is linear to at least  $2000 \text{ ng}\cdot\text{mL}^{-1}$ , with a limit of quantification of  $0.05 \text{ mg}\cdot\text{L}^{-1}$  and a coefficient of variation of 4.4% at  $0.2 \text{ mg}\cdot\text{L}^{-1}$ . Unbound levobupivacaine concentrations were determined after ultrafiltration.

#### **Quantification of human AAG in patient plasma**

Patient blood was centrifuged for 15 min at  $1000 \times g$  and aliquots of the plasma samples were stored at  $-80^\circ\text{C}$ . 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  $25^\circ\text{C}$ . 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  $1 \text{ mg.kg}^{-1}$  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 ( $C_{\text{max}}$ ) 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 ( $CU_{\text{max}}$ ) 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 ( $T_{\text{max}}$ ) were 30 (IQR, 25-40) min. In those infants who received a second spinal anaesthetic the mean  $C_{\text{max}}$  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 ( $CU_{\text{max}}$ ) was  $0.036 (16.1) \text{ }\mu\text{g.mL}^{-1}$  and the mean  $T_{\text{max}}$  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<sup>-1</sup>. 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<sub>max</sub> and T<sub>max</sub>. 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<sup>-1</sup> and 0.11-0.3 µg.mL<sup>-1</sup> 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<sub>u, max</sub>) rather than the total plasma concentration. In our study, the mean free C<sub>u, max</sub> 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<sup>-1</sup> (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<sup>-1</sup> did not produce clinical toxicity (13). An unbound levobupivacaine concentration in excess of 35 pg.mL<sup>-1</sup> 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<sup>-1</sup>) 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 ( $C_{\text{max}}$ ) 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 23<sup>rd</sup> April 2013

*Funding*; Funding was provided by Murdoch Childrens Research Institute grant (April 2013) and Anaesthetic departmental research funds.

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

**References:**

- 1 Mazoit JX. Pharmacokinetic/pharmacodynamic modeling of anesthetics in children: therapeutic implications. *Paediatric drugs* 2006; **8**: 139-150.
- 2 Kearns GL, Abdel-Rahman SM, Alander SW, *et al*. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *The New England journal of medicine* 2003; **349**: 1157-1167.
- 3 Neville KA, Becker ML, Goldman JL, *et al*. Developmental pharmacogenomics. *Paediatr Anaesth* 2011; **21**: 255-265.
- 4 Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. *Paediatr Anaesth* 2002; **12**: 205-219.
- 5 Ecoffey C, Desparmet J, Maury M, *et al*. Bupivacaine in children: pharmacokinetics following caudal anesthesia. *Anesthesiology* 1985; **63**: 447-448.
- 6 Desparmet J, Meistelman C, Barre J, *et al*. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. *Anesthesiology* 1987; **67**: 108-110.
- 7 Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. *Anesthesiology* 1988; **68**: 387-391.
- 8 Murat I. [Anatomic, physiologic and pharmacologic aspects of peridural and spinal anesthesia in pediatrics]. *Cahiers d'anesthesiologie* 1989; **37**: 357-364.

- 9 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of clinical epidemiology* 2008; **61**: 344-349.
- 10 Chalkiadis GA, Anderson BJ, Tay M, *et al.* Pharmacokinetics of levobupivacaine after caudal epidural administration in infants less than 3 months of age. *Br J Anaesth* 2005; **95**: 524-529.
- 11 Chalkiadis GA, Eyres RL, Cranswick N, *et al.* Pharmacokinetics of levobupivacaine 0.25% following caudal administration in children under 2 years of age. *Br J Anaesth* 2004; **92**: 218-222.
- 12 Luz G, Wieser C, Innerhofer P, *et al.* Free and total bupivacaine plasma concentrations after continuous epidural anaesthesia in infants and children. *Paediatr Anaesth* 1998; **8**: 473-478.
- 13 Bozkurt P, Arslan I, Bakan M, *et al.* Free plasma levels of bupivacaine and ropivacaine when used for caudal block in children. *European journal of anaesthesiology* 2005; **22**: 640-641.
- 14 Frawley G, Skinner A, Thomas J, *et al.* Ropivacaine spinal anesthesia in neonates: a dose range finding study. *Paediatr Anaesth* 2007; **17**: 126-132.
- 15 Frawley G, Smith KR, Ingelmo P. Relative potencies of bupivacaine, levobupivacaine, and ropivacaine for neonatal spinal anaesthesia. *Br J Anaesth* 2009; **103**: 731-738.
- 16 Frawley GP, Farrell T, Smith S. Levobupivacaine spinal anesthesia in neonates: a dose range finding study. *Paediatr Anaesth* 2004; **14**: 838-844.
- 17 Frawley G, Ragg P, Hack H. Plasma concentrations of bupivacaine after combined spinal epidural anaesthesia in infants and neonates. *Paediatr Anaesth* 2000; **10**: 619-625.
- 18 Anell-Olofsson M, Lonnqvist PA, Bitkover C, *et al.* Plasma concentrations of levobupivacaine associated with two different intermittent wound infusion regimens following surgical ductus ligation in preterm infants. *Paediatr Anaesth* 2015; **25**: 711-718.
- 19 Krylborn J, Anell-Olofsson ME, Bitkover C, *et al.* Plasma levels of levobupivacaine during continuous infusion via a wound catheter after major surgery in newborn infants: An observational study. *European journal of anaesthesiology* 2015.
- 20 Cortinez LI, Fuentes R, Solari S, *et al.* Pharmacokinetics of levobupivacaine (2.5 mg/kg) after caudal administration in children younger than 3 years. *Anesth Analg* 2008; **107**: 1182-1184.
- 21 Polaner DM, Taenzer AH, Walker BJ, *et al.* Pediatric Regional Anesthesia Network (PRAN): a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. *Anesthesia and analgesia* 2012; **115**: 1353-1364.
- 22 Suresh S, Long J, Birmingham PK, *et al.* Are caudal blocks for pain control safe in children? an analysis of 18,650 caudal blocks from the Pediatric Regional Anesthesia Network (PRAN) database. *Anesth Analg* 2015; **120**: 151-156.

- 23 Taenzer AH, Walker BJ, Bosenberg AT, *et al.* Asleep versus awake: does it matter?: Pediatric regional block complications by patient state: a report from the Pediatric Regional Anesthesia Network. *Regional anesthesia and pain medicine* 2014; **39**: 279-283.
- 24 Walker BJ, Long JB, De Oliveira GS, *et al.* Peripheral nerve catheters in children: an analysis of safety and practice patterns from the pediatric regional anesthesia network (PRAN). *British journal of anaesthesia* 2015; **115**: 457-462.
- 25 Bosenberg AT. Epidural analgesia for major neonatal surgery. *Paediatr Anaesth* 1998; **8**: 479-483.
- 26 Wood CE, Goresky GV, Klassen KA, *et al.* Complications of continuous epidural infusions for postoperative analgesia in children. *Can J Anaesth* 1994; **41**: 613-620.
- 27 Knudsen K, Beckman Suurkula M, Blomberg S, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507-514.
- 28 Dalens BJ, Mazoit JX. Adverse effects of regional anaesthesia in children. *Drug safety* 1998; **19**: 251-268.
- 29 Meunier JF, Goujard E, Dubousset AM, *et al.* Pharmacokinetics of bupivacaine after continuous epidural infusion in infants with and without biliary atresia. *Anesthesiology* 2001; **95**: 87-95.
- 30 Agarwal R, Gutlove DP, Lockhart CH. Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine. *Anesth Analg* 1992; **75**: 284-286.
- 31 McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesth Analg* 1992; **75**: 287-290.
- 32 Breschan C, Hellstrand E, Likar R, *et al.* [Early signs of toxicity and "subtoxic" conditions in infant monitoring. Bupivacaine plasma levels following caudal anesthesia]. *Anaesthesist* 1998; **47**: 290-294.
- 33 Hubler M, Gabler R, Ehm B, *et al.* Successful resuscitation following ropivacaine-induced systemic toxicity in a neonate. *Anaesthesia* 2010; **65**: 1137-1140.
- 34 Maxwell LG, Martin LD, Yaster M. Bupivacaine-induced cardiac toxicity in neonates: successful treatment with intravenous phenytoin. *Anesthesiology* 1994; **80**: 682-686.
- 35 Mollvaine WB, Knox RF, Fennessey PV, *et al.* Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. *Anesthesiology* 1988; **69**: 261-264.
- 36 Bachmann MB, Biscoping J, Adams HA, *et al.* [The significance of the sampling site in the determination of plasma levels of local anesthetics using 0.75% bupivacaine as an example]. *Regional-Anaesthesia* 1990; **13**: 16-20.

## 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  $1\text{mg}\cdot\text{kg}^{-1}$  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  $1\text{mg}\cdot\text{kg}^{-1}$  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  $1\text{mg}\cdot\text{kg}^{-1}$  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  $1\text{mg.kg}^{-1}$  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.

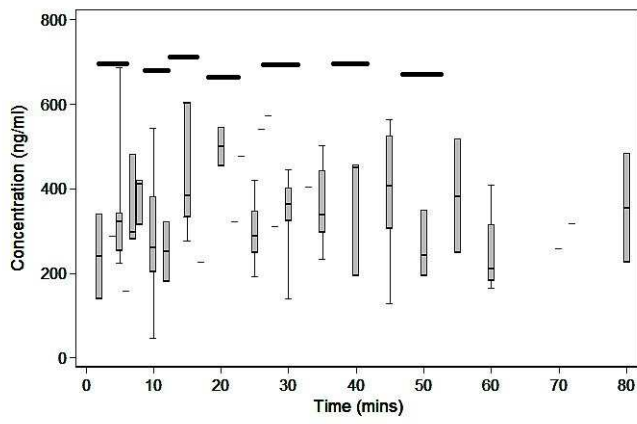
		Median	IQR
Total plasma Levobupivacaine $\mu\text{g.ml}^{-1}$	One Spinal	0.33	0.25-0.42
	Repeat Spinal	0.58	0.47-0.77
Unbound Levobupivacaine $\text{ng.ml}^{-1}$	One Spinal	19.5	14.5-38
	Repeat Spinal	37	24-48
Unbound Fraction		6.5%	4-9.6%
Alpha 1 Acid Glycoprotein $\text{g.l}^{-1}$		0.25	0.17-0.37
Albumen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

Table 2. Plasma concentrations following infant spinal anaesthesia with  $1\text{mg.kg}^{-1}$  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  $1\text{mg.kg}^{-1}$  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 <sub>T</sub> (µg.ml <sup>-1</sup> )	C <sub>U</sub> (µg.ml <sup>-1</sup> )	Presentation
<b>Single Block</b>	Caudal	7	Bupiv 2.5mg.kg <sup>-1</sup> Ad	1-6mo	0.97 (0.55-1.93)		No events
	Caudal	32	Bupivacaine 3.1mg.kg <sup>-1</sup> Ad	36-52wks	0.97 (0.56-1.62)		Abnormal EEG Jittery
<b>Continuous Infusion</b>	Caudal	13	Bupivacaine 0.25% Ropivacaine	10 mo-8yrs		Bupi 0.05 Ropi 0.06	No events
	Caudal	33	Ropivacaine 10mg.kg <sup>-1</sup>	Preterm	6 1.2(8hrs)		Ventricular arrhythmia
	Epidural	30	Bupivacaine 0.5 mg.kg <sup>1</sup> .hr <sup>-1</sup>	9yo	5.4		Seizure
	Intra-pleural	30	Bupivacaine 0.1 mg.kg.hr <sup>-1</sup>	3yo	5.6		Seizure
	Caudal catheter	34	Bupivacaine 0.1 mg.kg.hr <sup>-1</sup>	Term	5.6 3.7(12hr)		Ventricular arrhythmia
	Caudal		Bupivacaine 1ml.kg <sup>-1</sup>	Term	Lost		Ventricular arrhythmia
	Caudal	31	Bupivacaine 2.5mg.kg.hr	Term	5.6 3.7(12hr)		Ventricular arrhythmia
	Epidural		Bupivacaine 1.67 mg.kg.hr	8yo	6.6		Seizure

		Bupivacaine 1.67 mg.kg.hr <sup>-1</sup>	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 <sup>-1</sup>	6days-3mo	0.88 (0.46-1.47)	0.034 (0.02-0.07)	Jittery
Intra- pleural	35	Bupivacaine 1.25 mg.kg.hr <sup>-1</sup>		7.0		Asymptomatic

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



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