Disposition of levobupivacaine during intraoperative continuous caudal epidural analgesia in a preterm neonate

Jan Sipek[1], Pavla Pokorna[2,3,4], Martin Sima[2], Jitka Styblova[5], Vladimir Mixa[1]

Background. Continuous caudal epidural analgesia used intraoperatively in children is an effective and safe technique. However, in preterm neonates, developmental factors may significantly affect levobupivacaine disposition, leading to variable pharmacokinetics, pharmacodynamics, and potential large-variable systemic toxicity of local anesthetics.
Objective. To our knowledge, this is the first case report describing the disposition of levobupivacaine used for intraoperative caudal epidural analgesia in a preterm neonate treated for the postoperative pain profile.
Method. 4-days old neonate (postmenstrual age 35+5, weight 2140 g) with congenital anal atresia received continuous caudal epidural long-term analgesia (loading dose 1.694 mg/kg, initial infusion 0.34 mg/kg/hour) before correction surgery. The blood samples were obtained at 1.0, 1.5, 6.5, 12, and 36.5 h after the start of epidural infusion. The pharmacokinetic profile of levobupivacaine was determined by using the Stochastic Approximation Expectation Maximization algorithm. COMFORT and NIPS pain scores were used for the assessment of epidural analgesia.
Results. The levobupivacaine absorption rate constant, apparent volume of distribution, apparent clearance, and elimination half-life were 10.8 h^{-1}, 0.9 L, 0.086 L/h, and 7.3 h, respectively.
Conclusion. The results confirm our hypothesis of altered pharmacokinetics in the preterm neonate. Therefore, levobupivacaine therapy in these patients should be carefully monitored. Since therapeutic drug monitoring of levobupivacaine is not established in clinical routines, we suggest monitoring the intraoperative pain profile using validated scores.
Trial Registration: EudraCT number: 2020-000595-37

Key words: levobupivacaine, local anaesthesia, pharmacokinetics, neonates, dosing

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[1]Department of Anaesthesia, Resuscitation and Intensive Medicine, 2nd Faculty of Medicine, Charles University and Faculty Hospital Motol, Prague, Czech Republic
[2]Institute of Pharmacology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic
[3]Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic
[4]Department of Physiology and Pharmacology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
[5]Department of Paediatric Surgery, 2nd Faculty of Medicine, Charles University and Faculty Hospital Motol, Prague, Czech Republic
Corresponding author: Jan Sipek, e-mail: jan.sipek@fnmotol.cz

INTRODUCTION

Regional anaesthesia and a subsequent caudal block are considered effective and safe techniques used intraoperatively in the paediatric population[1]. Despite reports of local anaesthetic systemic toxicity (LAST) and some promising newer and safer techniques developed in this population[2,3], continuous caudal epidural long-term analgesia (c-CELA) is valid for use with background evidence, for example, for reasons of reducing the consumption of opioids and their potential side effects in the neonatal population[4]. Commonly used drugs for caudal analgesia are ropivacaine (0.1–0.375%) and levobupivacaine (0.125–0.25%), which are known to be better tolerated compared to racemic bupivacaine, can be used in neonates and with certain technical adjustments also in premature babies[5]. In general, levobupivacaine has a higher unbound clearance rate, shorter elimination half-life, smaller volume of distribution, and decreased affinity for brain and myocardial tissues than bupivacaine, which reduces the potential for interindividual variability. Levobupivacaine is absorbed after epidural administration from the epidural space into the blood with a time to peak concentration (T_{max}) of 30 min (similar to adults) to 50 min (prolonged in neonates vs adults). In the blood, levobupivacaine is bound mainly to alpha-1-acid glycoprotein (AAG) and to a lesser extent to albumin[6]. In neonates, the levels of albumin and AAG are significantly lower than in infants aged ≤ 1 year, the affinity of local anaesthetics for albumin is lower than in adults, and the unbound fraction of levobupivacaine, which is about 20%, is higher in neonates than in older children[7,8]. Elimination of levobupivacaine depends predominantly on protein binding, and on hepatic metabolism (CYP 3A7, CYP 3A4, and CYP 1A2); therefore, clearance (CL) of levobupivacaine is decreased in neonates and infants[6,9,10]. The hepatic extraction ratio of levobupivacaine is low (0.30–0.35). Body size and postnatal age (PNA) were found to be the covariates for the prediction of levobupivacaine CL (ref.[11]). We present the case of a premature neonate who intraoperatively re-

Table 1. Dosing adjustment of levobupivacaine in the form of a mixture (c-CELA) in a preterm neonate for continuous caudal epidural analgesia.

Time schedule hours (after the start of c-CELA)	0–3.5	3.5–27.5	27.5–33.5	33.5–39.5	39.5–45.5	45.5–51.5	51.5–57.5	57.5–66.5
Period	I	II	III	IV	V	VI	VII	VIII
Infusion rate mL/hour	0.30	0.25	0.22	0.20	0.18	0.15	0.10	0.05
Index mg/Kg/hour	0.334	0.278	0.245	0.222	0.2004	0.167	0.1113	0.0556

Table 2. Pharmacokinetics of levobupivacaine in a preterm neonate used for continuous caudal epidural analgesia.

Time schedule hours (after the start of c-CELA)	1.0	1.5	6.5	12.0	36.5
Period	I		II		IV
Cpl levobupivacaine ng/mL	339.00	303.00	241.00	497.00	631.00
Cpl-free levobupivacaine ng/mL	10.20	11.35	7.70	14.40	8.90

10 ng/mL = 0.01 μg/mL

ceived levobupivacaine for continuous caudal epidural analgesia at the Department of Anaesthesia, Resuscitation, and Intensive Medicine of the 2nd Faculty of Medicine of Charles University and Motol University Hospital, Prague, Czech Republic in April 2022. The aim of this report is to describe the levobupivacaine disposition and to monitor its efficacy and safety in the patient treated for acute postoperative (0–48 h after surgery) and prolonged (48 h) pain profiles. This report was approved by the Ethics Committee EC-1607/20 (LEVON clinical trial, EudraCT number: 2020-000595-37) in accordance with the latest Declaration of Helsinki.

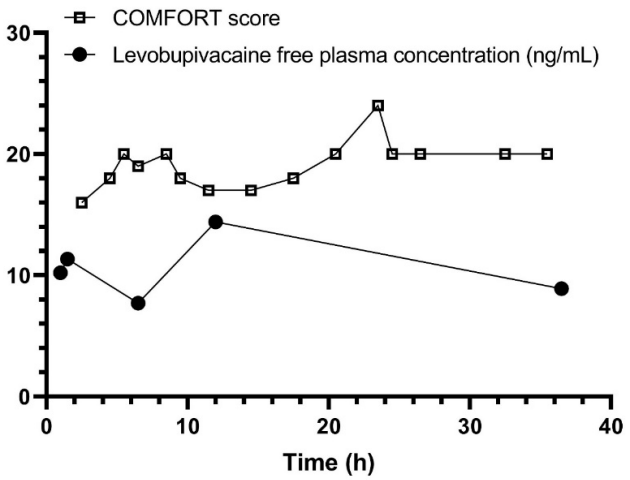

Fig. 1. Disposition of levobupivacaine during intraoperative continuous caudal epidural analgesia in a preterm neonate. CNS toxicity threshold is reported in the literature for 0.1–0.2 μg/mL unbound (10 ng/mL = 0.01 μg/mL for readers when converting units).

CASE REPORT

A 4-day-old premature female (postmenstrual age 35+5 weeks, actual weight 2140 g, length 44 cm) was referred from the Department of Neonatology, Institute for the Care of Mother and Child and 3rd Faculty of Medicine, Charles University, Prague, Czech Republic to the Department of Anaesthesia, Resuscitation and Intensive Medicine, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic for corrective surgery for congenital anal atresia with fistula. Laboratory parameters were measured: haemoglobin 173 g/L, serum creatinine 59.0 μmol/L, albumin 31.4 g/L, total protein 46.6 g/L, alanine transferase 0.41 μkat/L (0.0069 units/L), aspartate transferase < 0.15 μkat/L (0.0026 units/L), bilirubin 289.2 μmol/L except for AAG, which was not routinely measured.

Dosage of analgesic drugs

After induction of general anaesthesia, a caudal epidural catheter was inserted according to the local protocol. The patient received 1.45 mL (i.e., 1.694 mg/kg) of levobupivacaine 0.25% (Levobupivacaine Kabi 5 mg/mL and saline F1/1 0.9% diluted 1:1), subsequently followed by 0.34 mg/kg/hour (0.3 mL/hour) of levobupivacaine 0.238% (mixture of sufentanil 10 μg/2 mL, levobupivacaine 100 mg/20 mL and 20 mL of saline F1/1 0.9%) as an initial maintenance dose. The maintenance dose of levobupivacaine was adjusted (with a de-escalation from 0.334, 0.278, 0.245, 0.222, 0.2004, 0.167, 0.1113, and 0.0556 mg/kg/hour) according to the desired effects, and the rate of continuous infusion was reduced from 0.3 mL/h to 0.25, 0.22, 0.20, 0.18, 0.15, 0.10, and 0.05 mL/h, at 3.5, 27.5, 33.5, 39.5. 45.5. 51.5, 57.5 hours, and stopped at 66.5 hours (after initiation of the c-CELA infusion). Postoperatively, a maintenance dose of paracetamol 20 mg (9.35 mg/kg) was given intravenously (iv) every 6 h, while midazolam 3 x 0.3 mg bolus iv was given as rescue adjuvant therapy only during the first 24 h (ref.[12,13]).

Samplings and pharmacokinetics

Plasma samples (0.2–0.5 mL) were separated from blood samples according to the WHO recommendations for further analysis by liquid chromatography with tandem mass spectrometry in positive ESI mode [Nexera X2 Shimadzu HPLC (Nakagyo-ku, Kyoto, Japan) with AB Sciex QTRAP 5500 (MA, USA)] using centrifugal filters (Amicon Ultra 0.5 mL, Merck Millipore Ltd., Cork, Ireland) for free levobupivacaine plasma concen-

trations[14]. Analysis was performed on the Zorbax Eclipse XDB-C18 column (1.8 µm, 50x4.6 mm). Total levobupivacaine plasma concentrations (339.00, 303.00, 241.00, 497.00, and 631.00 ng/mL) and free levobupivacaine plasma concentrations (10.20, 11.35, 7.70, 14.40, and 8.90 ng/mL) were determined after 1.0, 1.5, 6.5, 12.0 and 36.5 h after initiation of the c-CELA infusion. The median (IQR) value of levobupivacaine binding to plasma proteins was 97.0 (96.8–97.1) %. The pharmacokinetic parameters of levobupivacaine were estimated based on levobupivacaine dosing and the plasma concentration-time profile by maximum likelihood using the Stochastic Approximation Expectation Maximization (SAEM) algorithm within Monolix Suite software version 2021R1 (Lixoft SAS, Antony, France). One-compartmental model with first-order absorption and elimination best fits LB concentration-time data. The model was parametrized in terms of the absorption rate constant (K_a), apparent volume of distribution (Vd/F), and apparent clearance (CL/F). Elimination half-life ($t_{1/2}$) was calculated as $t_{1/2}=0.693\times(Vd/F)/(CL/F)$. The calculated pharmacokinetic parameters of levobupivacaine in our patient were as follows: $K_a=10.8\ h^{-1}$, Vd/F=0.9 L, CL/F=0.086 L/h and $t_{1/2}=7.3$ h.

Efficacy and safety

The COMFORT Score and the Neonatal Infant Pain Score (NIPS) were used for assessments and reassessments of stress/pain management[15]. COMFORT score values between 15 and 27 indicate no pain or stress, while values over 27 indicate significant pain or stress requiring an extra dose of analgesic and sedative drugs. Score values below 15 in sedated infants indicate oversedation. NIPS was assessed after extubating. A score between 0–3 means no or moderate pain. A value of 4 or greater indicates significant pain requiring an extra dose of analgesics or sedation. The mean (SD) COMFORT score was observed to be 19.13 (1.86) and was zero for NIPS. The safety parameters of levobupivacaine were observed (i.e., hemodynamic status such as bradycardia<80/min, arrhythmia, respiratory and CNS status – clinical seizures).

Outcome parameters

The patient was extubated after 37 h, transferred to the referral maternal/neonatal hospital after one week, and later discharged. A follow-up neurological examination was within normal range. However, a unilateral severe hearing loss (over 30 dB loss) was detected during follow-up more than eight months after hospital discharge and is expected to be unrelated to c-CELA administration. No signs of toxicity related to intraoperative and prolonged levobupivacaine analgesia or other complications associated with c-CELA administration were reported. Additionally, no persistent sign of pain was observed in the preterm neonate.

DISCUSSION

This case report is an example from daily clinical practice that demonstrates the effective and safe use of levobupivacaine administered intraoperatively (during the acute postoperative period lasting 48 h and for long-term care > 48 h) in the premature neonate. Pain management was successful in the patient using the c-CELA infusion and adjuvant analgesia and sedation (paracetamol and midazolam) based on the validated scores (COMFORT and NIPS). No adverse drug reactions related to intraoperative analgesia were observed. In our case, opioids were used only as an analgesic mixture (c-CELA infusion), while paracetamol and midazolam were administered regularly and as a rescue medication, respectively, in case of patient discomfort.

At the same time, this is the first published case report on the levobupivacaine disposition in a preterm neonate reflecting that free and total levobupivacaine plasma concentrations were below the toxic range with the use of an evidence-based levobupivacaine dosing regimen optimized for the premature population; however, data on dose adjustments are sparse. This may be important, because target therapeutic and toxic levels are difficult to use in practice for local anaesthetics[16,17].

In our patient, we observed approximately a 2-fold longer elimination half-life than in adults, and even compared to infants the clearance was significantly reduced[10,18]. This observation is also consistent with the expected lower functional capacity of CYP 3A4 and CYP 1A2 due to immaturity in preterm neonates. The protein binding of levobupivacaine is reported to be higher than 97% in adults[18]. Although the rate of bound levobupivacaine in our patient was almost the same (IQR: 96.8–97.1%), possibly due to lower plasma protein levels in preterm neonates, the free fraction of the drug may be higher and this may be associated with a risk of toxicity. In addition, other factors, such as changes in AAG during inflammation or after surgery, as well as hypoxia, acidosis, and hypothermia, can lead to changes in pharmacokinetics or increased cardiac toxicity. For example, the pharmacokinetic model showed that in infants aged from 3 to 6 months, the steady state of unbound levobupivacaine concentration was achieved at 0.03 µg/mL for the caudal epidural route with a loading dose of 2 mg/kg and an infusion rate of 0.2 mg/kg/h (ref.[19]). Studies in adult volunteers have shown a CNS toxicity threshold of 2–3 µg/mL in total and 0.1–0.2 µg/mL of unbound bupivacaine, levobupivacaine, and ropivacaine[6,8,20]. Threshold plasma concentrations for cardiac toxicity are higher than for CNS.

CONCLUSION

In our case, the measured levobupivacaine plasma concentrations were below the toxic range for unbound and total levobupivacaine levels as reported[6], while the effectiveness score was within the therapeutic range and

well-tolerated in the preterm neonate. All the above facts suggest that the initial and maintenance doses of levobupivacaine should be individualized in this population and that levobupivacaine pharmacotherapy should be carefully monitored and optimized as previously[21,22].

Since therapeutic drug monitoring in the sense of measuring levels and their interpretation is not established in practice for local anaesthetics and the values of the therapeutic ranges for these drugs are also not unequivocally established, monitoring and management of the intraoperative pain profile with validated scores is essential for the adjustment and optimization of therapy.

ABBREVIATIONS

AAG, Alpha-1-acid glycoprotein; c-CELA, Continuous caudal epidural long-term analgesia; CNS, Central nervous system; CL, Clearance; CL/F, Apparent clearance; CYP, Cytochrome P450; IQR, Interquartile range; iv, Intravenously; K_a, Absorption rate constant; LAST, Local anaesthetic systemic toxicity; NIPS, Neonatal Infant Pain Score; PMA, Postmenstrual age; PNA, Postnatal age; SAEM, Stochastic Approximation Expectation Maximization; SD, Standard deviation; T_{max}, Peak concentration; $t_{1/2,}$ Elimination half-life; Vd/F, apparent volume of distribution.

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