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CLINICAL STUDY

Plasma concentrations of levobupivacaine in neonates during caudal epidural analgesia maintained over 48 hours

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ABSTRACT

BACKGROUND: Differences in neonatal pharmacokinetics are known to cause systemic accumulation of levobupivacaine with adverse effects during epidural analgesia. Therefore, it is not recommended to surpass 48 hours of administration in neonates. Free and total levobupivacaine levels are considered as predictors of toxicity.

OBJECTIVE: The aim of the LEVON pilot study was to detect the accumulation of levobupivacaine during epidural analgesia exceeding 48 hours in neonates.

METHODS: Ten neonates received a loading dose of levobupivacaine (1.25 mg/kg) followed by a continuous infusion (0.2 mg/kg/hour) epidurally. Free and total levobupivacaine concentrations were measured 0.5, 1, 6, 12, 36, 72 and 144 hours after the start of infusion. Cumulative doses of levobupivacaine, pain scores and clinical signs of toxicity were used for assessing efficacy and safety.

RESULTS: The median concentrations of total levobupivacaine were 586.0, 563.0, 837.5, 957.0, 1930.0, 708.5 and 357.5 ng/ml. The median concentrations of free levobupivacaine were 4.0, 3.6, 5.5, 3.6, 5.5, 0.8 and 0.0 ng/ml. Three patients reached concerning concentrations of total levobupivacaine. Levels of free levobupivacaine remained low. No signs of toxicity were observed.

CONCLUSION: Caudal epidural analgesia with levobupivacaine lasting longer than 48 hours appears to be safe providing that free levobupivacaine levels are below the presumed threshold for toxicity *(Tab. 1, Fig. 1, Ref. 29)*. Text in PDF *www.elis.sk*

KEY WORDS**:** free levobupivacaine, total levobupivacaine, neonate, caudal continuous epidural analgesia, postoperative pain.

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Introduction

Levobupivacaine is one of the most commonly used local anesthetics (LA), a drug for regional intra- and post-operative applications of epidural analgesia in full-term neonates. Levobupivacaine seems to be less cardio- and neurotoxic, and equally potent LA in comparison to its racemate (bupivacaine) (1). Although its effectiveness is known, available data about the safety parameters in this population are scarce. Despite advances in perioperative analgesia in neonates (use of new drugs such as dexmedetomidine, catheter in the wound (2), peripheral blocks) (3), caudal continuous epidural long-term (longer than 48 hours) analgesia still offers significant advantages. It improves pain management, especially in patients needing extensive corrective surgeries (in some congenital disorders) or other conditions with challenging analgesia in the urogenital or abdominal areas (necrotic enterocolitis). Other substantial benefits include hemodynamic stabilization and opioids adverse effects (AE) reduction (4–7) due to lower consumption.

Epidurally administered LA is partially absorbed into the bloodstream and primarily bound to plasma proteins (albumin and alpha-1-acid glycoprotein (AAG)) (8). Both free (unbound) and total (unbound and bound together) levobupivacaine concen-

trations are markers of cardiotoxicity and neurotoxicity, although the threshold is poorly defined in neonates due to scarcity of data. The possibility of cumulation of levobupivacaine is a serious concern considering the differences in neonatal pharmacokinetics (decreased liver or kidney function proportionally to immaturity, lower albumin and AAG, different volume of distribution) (9–11). Therefore, maintaining epidural infusion should not exceed 0.2 mg/kg/hour. It is generally not recommended to be maintained for a period longer than 48 hours (12). Part of the LEVON study (Pharmacokinetics and pharmacodynamics of levobupivacaine during continuous caudal epidural analgesia in neonates) protocol describes regular measurement of plasma levels of total and free levobupivacaine levels. After successful enrollment of the first ten patients, the first interim analysis was performed (a pilot study).

The aim of this original prospective preliminary analysis was to determine the possible toxic systemic accumulation of levobupivacaine during epidural analgesia in mature neonates.

Methods

After obtaining informed consent and approval from local authorities (ethical committees, State Department for Drug Control in the Czech Republic, study protocol number 1111111, EudraCT number 2020-000595-37), neonates meeting the inclusion criteria were further analyzed from May to November 2021. The inclusion criteria were as follows: indication for epidural analgesia longer than 48 hours by attending physician and successful insertion of epidural catheter, PMA (postmenstrual age) of 37–45 weeks, no known impairment of liver or kidney function, no spinal defects, no coagulopathy or anemia, blood samples obtained after 48 hours of epidural infusion.

The epidural catheter was inserted via "caudal approach" (needle G18, G20 catheter, Arrow Int., USA) before surgery in general anesthesia (sevoflurane, sufentanil, cisatracurium) or after the surgery in analgosedation (midazolam, morphine). According to the protocol of the study, levobupivacaine 0.25 % initial dose (Chirocaine 5 mg/ml, Inj. Sol., 5x10 ml, AbbVie – Italy) 1.25mg/kg was followed by maintaining infusion of 0.2 mg/kg/hour combined with sufentanil 0.02 mcg/kg/hour (Sufentanil Torrex 5microgram/ml, 5x2 ml, Piramal Critical Care V.S Rouboslaan, Netherland).

Achieving the optimal score of points (COMFORT-neo scale in intubated patients (13) and Neonatal Infant Pain Scale (NIPS) in extubated patients) (14) allowed a reduction in opioids (morphine infusion) or sedatives (midazolam infusion) according to the attending physician. Otherwise, a bolus of morphine was administered, or the dose of the analgesic drugs was increased.

Patients were monitored for signs of convulsions, muscle spasms or arrhythmias signaling the possible early signs of toxicity during epidural analgesia.

Blood samples (0.2–0.5 ml) were obtained after 0.5, 1, 6, 12, 36, 72 and 144 hours into the start of epidural infusion. Unplanned last blood sample was obtained just before the removal in case of earlier removal of the catheter. Blood samples were stored in a refrigerator before further analysis for seven days at maximum.

Subsequently, after separating the plasma, total and free levobupivacaine concentrations were determined by liquid chromatography-tandem mass spectrometry in positive electrospray ionization (ESI) in mode (LC-ESI(+)-MS/MS). Mepivacaine was used as internal standard (IS). Plasma was spiked with an internal standard solution, then precipitated with acetonitrile and subsequently measured after the centrifugation. Centrifugal filters (Amicon Ultra 0.5 ml, Merck Millipore Ltd., Cork, Ireland) were used for extracting free levobupivacaine. The method was developed using Nexera X2 Shimadzu HPLC (Nakagyo-ku, Kyoto, Japan) coupled with AB Sciex QTRAP 5500 (MA, USA). The analysis was performed using Zorbax Eclipse XDB-C18 column (1.8 µm, 50 x 4.6 mm). The method was evaluated by meeting all necessary criteria and requirements for the Scientific Working Group for Forensic Toxicology (15).

Results

Ten patients were enrolled while six patients were excluded from this pilot study in the initial phase and subsequently from this analysis for reasons as follows: two cases of failed insertion or malfunction of epidural catheter, one case of early removal of the catheter causing leakage around the puncture site and three cases of mistakes during blood sample handling (forgetting to obtain them, errors in storing or laboratory method).

Demographic data (Tab. 1) were collected from ten mature neonates. The postoperative epidural analgesia was assessed as efficient.

Tab. 1. Demographic data.

Patient	Weight (g)	Gender	PMA (Post-menstrual age) (Weeks + days)	PNA (Post-natal age) (days)	Extubation time after the start of epidural infusion (hours)	Duration of epidural infusion (hours)	Indication of caudal epidural analgesia
1	3400	M	42+0	7	11	81	Hirschsprung disease
2	3185	M	39+1	7	7	72	Anal atresia
3	3365	M	40+5	12	17	84	Hirschsprung disease
4	4010	M	43+0	14	22	70	Abdominal neuroblastoma
5	2980	M	37+0	7	9	55	Hirschsprung disease
6	2948	M	39+0	7	37	63	Retroperitoneal malignant neoplasia
7	3500	M	42+1	5	92	191	Diaphragmatic hernia
8	3300	M	40+2	7	138	163	Diaphragmatic hernia
9	3200	F	38+1	3	63	86	Diaphragmatic hernia
10	2550	F	39+0	7	157	146	Diaphragmatic hernia

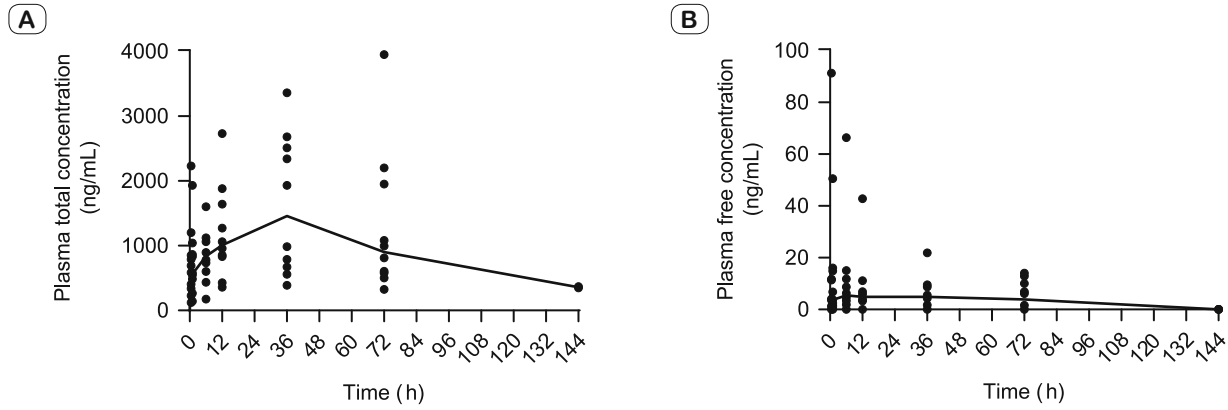

Fig. 1. Plasma total (a) and free (b) levobupivacaine concentrations-time profiles in ten neonates after levobupivacaine epidural analgesia. The black lines represent median values. The blood samples, obtained out of the schedule, were analyzed precisely as described in the text, but graphically (GraphPad) are represented to the nearest planned value.

Only one patient (No. 8) needed increased doses of morphine and midazolam during the first 12 hours after the start of epidural insertion. Substantially decreased doses of opioids could have been the reason for a reduced infusion rate of epidural infusion, according to the attending physician or in line with work patterns of the ward. The median time of extubation was 30 hours (range 7–157 hours) after the start of epidural analgesia with median duration of 84 hours (range 55–191hours). In one case the catheter was removed due to a significant leakage of mixture around the puncture site (patient No. 6). Otherwise, the main reason for extracting the catheter was no further clinical use. During the observation period, no clinical signs of neurotoxicity or cardiotoxicity were detected. Mild peripheral paraparesis (patient No. 7) was reported two months after the end of the observation period, which was not associated with epidural infusion according to the attending physician and reporting neurologist. Neurological findings were repeatedly assessed as physiological during the epidural use.

When there was no further use for epidural analgesia close to the scheduled blood draw, an extra blood sample was obtained with epidural catheter removal. The last blood samples of patients No. 5, 6, 4 were obtained 55 hours, 63 hours and 70 hours after the start of epidural infusion. Several mistimed blood draws have been observed during data processing due to human factor. Patient No. 1 had the blood drawn after 3 hours (instead of half an hour), patient No. 8 24, 60 and 132 hours (instead of 36, 72 and 144 hours) and patient No. 9 24 hours (instead of 12 hours) after the start of epidural analgesia.

The median plasma concentrations of total levobupivacaine (Fig. 1a) were 586.0 (range: 123.0–2230.0), 563.0 (range: 140.0–1930.0), 837.5 (range: 175.0–1600.0), 957.0 (range: 358.0–1880.0), 1930.0 (range: 557.0–3360.0), 708.5 (range: 501.0–2200.0) and 357.5 (range: 348.0–363.0) ng/ml in blood sample taken 0.5, 1, 6, 12, 36, 72 and 144 hours into the start of caudal epidural analgesia, respectively. The maximum concentration of 3950.0 ng/ml was achieved 63 hours after the start of epidural infusion (before planned catheter extraction) in patient No. 6.

The median plasma concentrations of free levobupivacaine (Figure 1b.) were 4.0 (range: under limit of quantification (LOQ) –91.3), 3.6 (range: under LOQ –50.5), 5.5 (range under LOQ –66.4), 3.6 (range: under LOQ –11.1), 5.5 (range: under LOQ –21.9), 0.8 (range: under LOQ –14.0) and 0.0 (range: under LOQ) ng/ml after 0.5, 1, 6, 12, 36, 72 and 144 hours into the start of caudal epidural analgesia, respectively. The maximum concentration of 91.3 ng/ml was measured 0.5 hours after the start of epidural infusion in patient No. 9. All measured free levobupivacaine plasma concentrations in patients No. 7 and 8 were under LOQ (except 1.0 ng/ml at 1 hour in patient 8) and therefore could not be recorded (Fig. 1b).

Discussion

Ongoing safety monitoring, including analysis of measurement results, is a standard part of clinical trials. This original pilot study brings valuable and rare information about therapy with a potentially toxic drug in this rare group of patients. To our knowledge, this is the first study to measure total and free levobupivacaine levels in neonates during epidural analgesia exceeding 48 hours.

For ethical reasons and number of scheduled blood samples, the volume of each blood sample was adjusted for this age group to 0.2–0.5ml to meet the maximal limits of blood drawing in neonates in accord with the recommendations of WHO (16). Small amounts of material without the possibility to repeat the measurement led to failed laboratory analysis in three cases (determination of plasma free levobupivacaine after 0.5 hour in patients No. 2 and 3 and plasma concentration of total levobupivacaine after 132 hours in patient No. 8). Two patients were excluded from the study due to a combination of missing or spurious data. There was not enough material for determinng plasma AAG concentration. This acute-phase protein (along with albumin) binds with free bupivacaine substantially (17). An increase in plasma AAG levels during the stress response (e.g., surgery) (18) is considered responsible for

the increase in total levobupivacaine, while the free fraction remains relatively unchanged (19, 20). It suggests a protective effect of increasing AAG levels (16, 21).

Although average daily doses of morphine increased in patient No 8. between 24–48 hours temporarily, the reduced daily doses of systemic opioids and sedatives for the rest of the patients suggest the efficacy of recommended doses for epidural analgesia in mature neonates (levobupivacaine 0.25 %, initial dose 1.25 mg/kg with the maintenance infusion of 0.2 mg/kg/hour).

With a maximum of 91.3 ng/ml, all measured levels of free levobupivacaine were well below the presumed central nervous toxicity threshold of free bupivacaine (200–300 ng/ml) (21, 22). The plasma concentration of free levobupivacaine as a target for the prevention of toxicity remains unclear. Medians of free levobupivacaine levels after 72 and 144 hours (two samples in total, with values under the limit of quantification) into the start had a decreasing trend.

Medians of total levobupivacaine concentrations increased up to 36 hours (four out of ten patients had a decreasing trend of total levobupivacaine) already after the start of epidural analgesia. Subsequent measurements (after 72 and 144 hours) in all patients, except for patient No. 6 (described below), showed decreasing trends in plasma concentrations.

This suggests a steady state within 72 hours without further accumulation of levobupivacaine. Unexpectedly in patient No. 6, who had the peak concentrations of free and total levobupivacaine levels were determined from the last blood sample provided earlier (63 hours after the epidural start) with catheter removal due to leakage around the catheter. Although the peak of free levobupivacaine remained low (12.1 ng/ml), total levobupivacaine levels were 3360.0 ng/ml and 3950.0 ng/ml after 36 h and 63 h, respectively which exceeded the presumed line of levobupivacaine neurotoxicity, namely 2620.0 ng/ml (23). Signs of cardiotoxicity or neurotoxicity were not observed in the cohort. Subsequent control discovered the initial load of levobupivacaine to be higher by 23.0 % with an initial maintaining speed of 0.24 mg/kg/hour, which was decreased progressively. Thus, the total administered dose was lowered proportionally. The deviations from intended dose were +15.2 %, +7.8 % higher and –3.8 % lower after 36, 48 and 63 hours into the start of the epidural infusion. This would suggest an early cumulation, rather than the late one. Other contributing factors could be accidental, such as not recorded overdose, hypoalbuminemia (28.8 g/l) and acquired impaired liver function after initial surgery (extrarenal retroperitoneal abdominal neoplasm extirpation). The relevance of concomitant diseases (gastroesophageal reflux, bicuspid aortic valve, patent *foramen ovale*) is unknown. The relatively low rise of levobupivacaine levels might be explained by stress-induced production of AAG.

Patients No. 5 and 9 also exceeded the above-mentioned neurotoxic threshold, yet without any presence of toxic signs. It is important to note that the determination of the toxic level of levobupivacaine in serum is questionable, especially in neonates. The main reason is the lack of data. Bardsley et al (23) is the only study determining total levobupivacaine toxicity in adult volunteers. A dose of levobupivacaine was administered intravenously for 2–15 minutes until any clinical sign of toxicity appeared or reached a maximum dose of 150 mg. Adults may differ from the neonatal group due to substantial differences in metabolism (9) and clearance (11, 24) of levobupivacaine. Other factors that may be responsible for the higher tolerance (toxicity threshold) are the presumed delayed absorption from the epidural space to the intravenous compartment and enhanced production of AAG during stress (18–20) In the earlier studies, the line for bupivacaine toxicity varied between 2,000–10,000 ng/ml in children (25–27), making the free concentration of levobupivacaine (or bupivacaine) a more specific marker of toxicity. The concentration of free bupivacaine (or levobupivacaine) under the narrow threshold of 200–300 ng/ml (21, 22) combined with supposedly dangerous levels of total bupivacaine were not associated with signs of toxicity (21), which supports our study findings.

According to current recommendations, epidural analgesia in neonates should not exceed 48 hours (12). The main reason is the concern about the toxic accumulation of levobupivacaine. In this study, peak concentrations of free and bound levobupivacaine reached an equilibrium state in between 12 and 72 hours., with the exception of patient No. 6 due to the early removal of the catheter (after 63 hours). Total and free levobupivacaine concentrations were at their peak at this time. All subsequent values with the median concentration 72 hours and 144 hours into the epidural start had a decreasing trend. Only two samples were determined successfully at 144 hours. These data support using caudal epidural analgesia longer than for 48 hours in mature neonates with caution. This suggestion has been recently published in a study on a group of infants aged 3–6 months (28).

Despite low levels of free levobupivacaine and missing of any toxic adverse effects, safety should still be assessed with caution. To recognize early signs in neonates is a challenge due to their immature central nervous system and possibly suppressed toxicity under sedation (midazolam) (29). Significant inter-individual variability in this vulnerable population leads to a higher chance of overdose with extremely serious consequences.

This study has limitation, primarily due limited number of patients, while another significant limitation lies in limited blood sample size as discussed above.

Conclusion

In conclusion, caudal epidural analgesia with levobupivacaine exceeding 48 hours appears to be safe in mature neonates without known hepatic or renal impairment. No clinical signs of toxicity were recorded. The levels of free levobupivacaine were below the presumed threshold of toxicity. This allows for continued enrollment of patients in the LEVON study. Naturally, this must be performed with great caution. In terms of future safety assessment, free levobupivacaine measurement could be preferred over total levobupivacaine. Higher concentrations of total levobupivacaine might be tolerated if levels of free levobupivacaine stay lower than the above-discussed toxic levels.

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