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Effect of morphine and tramadol on serum levels of lidocaine after epidural administration in dogs

Alan Maksimović [1, *], Selma Filipović [1], Ismar Lutvikadić [1], Nataša Brajenović [2] and Irena Brčić Karačonji [2]

[1] Department of Clinical Science, Veterinary faculty, University of Sarajevo, Bosnia and Herzegovina
[2] Institute for Medical Research and Occupational Health, Ksaverska cesta 2, POB-291, HR-10001 Zagreb, Croatia

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Abstract

The objective of this study was to evaluate whether the addition of morphine or tramadol to lidocaine influences serum lidocaine concentrations in dogs administered these drugs epidurally prior to elective orchiectomy or ovariohysterectomy. Thirty dogs were divided into three groups of 10 each, with equal numbers of females and males. One group received epidurally 2% lidocaine combined with 0.9% NaCl, another received 2% lidocaine combined with morphine, and a third group received 2% lidocaine combined with tramadol. Blood samples for the determination of serum lidocaine concentrations were taken 10, 30, 60 and 90 min after epidural administration. Serum lidocaine concentrations were measured by gas chromatography-mass spectrometry (GC-MS). There was a total of 120 serum samples obtained. In most animals a peak serum lidocaine concentration was detected ten minutes after epidural administration. There were no significant differences in the detected serum lidocaine concentrations within observed groups of animals, or between males and females. Therefore, results suggest that morphine and tramadol can be used as additives to epidural lidocaine in dogs at the investigated doses, without significantly influencing lidocaine absorption from the epidural space and its serum concentration.

Key Words: dog, epidural anaesthesia, lidocaine serum concentration

Introduction

Analgesic efficiency of addition of the opioids to local anaesthetics for epidural anaesthesia (EA) is well documented in human and animal studies. Furthermore, it is defined that the local anaesthetics and opioids in combination for epidural anaesthesia manifest physical and chemical compatibility[4], and thus, they may be admixed for clinical use in regional anaesthesia. The commonly used epidural anaesthetic is lidocaine[5,6]. However, lidocaine is associated with a significant, dose-dependent potential for cardiovascular and central nervous system toxicity[5,9]. Systemic toxicity results from increased serum concentrations above a threshold level, commonly seen as an outcome of direct intravascular injection or systemic absorption

* Corresponding author: Alan Maksimović; Department of Clinical Science, Veterinary faculty Sarajevo, University of Sarajevo, Zmaja od Bosne 90. Sarajevo 71000, Bosnia and Herzegovina
E-mail address: alan.maksimovic@vfs.unsa.ba
Telephone: + 387 61 460 798
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from a tissue depot[10]. Addition of opioids to epidural local anaesthetics provides more potent and prolonged analgesia[12]. The analgesic potency of epidural administration of lidocaine, alone or in combination with tramadol or morphine, in dogs was investigated by Almeida *et al.*[1]. However, limited data are available to aid clinicians in determining whether admixing morphine or tramadol with epidural lidocaine can influence lidocaine resorption from epidural space, and therefore his serum concentration. Gusak *et al.*[5] provided preliminary results for lidocaine serum concentrations following epidural administration of lidocaine in combination with morphine in the rabbit. To the best of our knowledge, there have been no comparable studies conducted in the dog. Moreover, we have not found any reports on the influence of epidural administration of tramadol combined with lidocaine on serum lidocaine concentration. Hypothetically, morphine histamine induced vasodilatation[3], in contrast to tramadol which does not release histamine[2], can influence absorption of lidocaine from epidural space, and therefore its serum concentration[5,8]. The aim of this study was to evaluate the influence of adding morphine or tramadol to epidurally administered lidocaine on serum lidocaine concentration in the dog.

Materials and Methods

This work was approved by the ethics committee of the University of Sarajevo Veterinary Faculty. The study involved 30 clinically healthy dogs (ASA I-II), 15 males and 15 females, of multiple breeds, 19.6 ± 11.3 months old (18.4 ± 12.3, 20.5 ± 8.7 and 19.8 ± 13.4 months in the L, LT and LM groups, respectively) and weighing 16.5 ± 5.7 kg (13.5 ± 3.7, 15.9 ± 3.8 and 20.0 ± 7.2 kg in the L, LT and LM groups, respectively). In all dogs' food was withheld minimally eight hours prior to surgery, while water was available *ad libitum*. They were randomly divided into three groups of ten, with equal numbers of males and females represented in each group. The dogs received epidurally 4 mg/kg of lidocaine (lidokain hidrohlorid 2%, Galenika, Serbia) combined with 0.01 mL/kg of 0.9% NaCl in group L, 0.1 mg/kg of morphine (morphini hydrochloridum 20 mg/mL, Alkaloid, Macedonia) in group LM or 1.0 mg/kg of tramadol (TramadolSTADA 100 mg/2 mL, STADA Arzneimittel AG, Germany) in group LT. Total immobilization for epidural injections was achieved through induction of general anaesthesia with a bolus mixture of 5 mg/kg of ketamine hydrochloride (Ketaminol™ 10, Intervet International B.V., Netherlands) and 1 mg/kg of xylazine (Xylazin Bio 2%, Bioveta, Czech Republic) administered over the right cephalic catheter. The dogs were intubated and EA was performed as described by Valverde[12] by the same anaesthetist on each patient with the animal in sternal recumbency. Correct positioning of the needle was confirmed by the absence of cerebrospinal fluid or blood at the hub, hanging drop technique and lack of resistance to air and drug injection[7,11,12]. The animals were maintained in sternal position for 20 minutes after injection to provide uniform distribution of the drugs[1]. Efficiency of epidural anaesthesia was confirmed by anal sphincter relaxation and absence of anal sphincter movement on the palpation. Surgical plane of anaesthesia was maintained subsequently with intravenous ketamine and xylazine to effect. Depth of anaesthesia was subjectively evaluated by assessment of the muscular tonus of the jaw, pupils dilatation, eyeballs position, response to surgery and monitored physiological parameters (heart rate, respiratory rate, arterial hemoglobin oxygen saturation and non-invasive oscillometric arterial blood pressure). All surgeries were performed by the same surgeon. Throughout the surgical procedure sterile saline solution (10 mL/kg/h) was applied to all animals over the right cephalic catheter. Post epidural recovery of the motor and sensory functions of rear extremities was tested by mild clamping stimulus on the hind limbs at 5-minute intervals. Blood samples for determination of serum lidocaine concentration were collected over the left cephalic catheter into non-heparinized tubes 10, 30, 60 and

90 minutes after epidural administration. Catheter was flushed with 3 mL of sterile saline following each sample collection. The concentration of serum lidocaine was measured by gas chromatography-mass spectrometry (GC-MS)[14]. Briefly, Bond Elut LRC-Certify columns for solid phase extraction (SPE), 130mg (Agilent Technologies, Santa Clara, USA) were conditioned with 2 mL of methanol and 2 mL of a 0.1 M phosphate buffer (pH 6.0). Serum (0.5 mL) was mixed with 2 mL 0.1 M phosphate buffer (pH 6.0) and poured onto the conditioned columns. After column rinsing (6 mL deionised water followed by 0.3 mL of 0.1M hydrochloric acid and 9 mL of methanol) and drying under vacuum (5 min), the analyte was eluted with a mixture of dichloromethane:2-propanol:ammonium hydroxide (80:20:2, v/v/v). The eluents were collected in glass tubes and evaporated to dryness under a stream of nitrogen at 40 °C. The dry residue was dissolved in 100 µL of ethyl acetate and 1 µL of extract was is injected in the GC/MS. Samples were analysed with a Varian 3400 CX GC with Saturn 4D ion trap mass spectrometer in the electron impact mode. A HP-5MS (Agilent Technologies, Santa Clara, USA) capillary column (5% diphenyl-95% dimethylpolysiloxane) (30m x 0.25 mm id, 0.25 mm film thickness) was used. Quantitation ion for lidocaine was m/z 86. The precision of the method expressed as RSD was < 10% with recovery rate > 97%. Limit of detection was 2 ng/mL. Pharmacokinetic parameters (peak plasma concentration (Cmax), time to peak plasma concentration (Tmax), area under the curve from 0 to the 90 minutes ($AUC_{0-1.5}$), and elimination half-life (T1/2) were estimated using noncompartmental assumptions.

Normality of data distribution and equal variance between groups was confirmed by Shapiro-Wilk and Leven's tests. Serum lidocaine concentrations in the observed groups (L, LT and LM) were compared for statistical difference by way of a one-way ANOVA test. A t test was used to analyse the presence of any difference in detected serum lidocaine concentrations between males and females. A $P < 0.05$ was considered significant.

Table 1. Pharmacokinetic Parameters of lidocaine: Tmax (min), Cmax (µg/ml), $AUC_{0-1,5}$ (µg/mL*h) and T1/2 (h) for observed groups of animals.

Group	Tmax	Cmax	AUC	T1/2
Lidocaine	10	2.013	1.858	0.912
Lidocaine+Morphine	10	1.653	1.937	1.398
Lidocaine+Tramadol	10	1.737	1.820	0.689

Results

Surgical procedures did not last longer than 20 minutes. The mean (± SD) duration of orchiectomy was 9 ± 2 minutes, while for the ovariohysterectomy was 16 ± 4 minutes. No differences were recorded in monitored physiological parameters between observed groups of animals. Post epidural recovery of the motor and sensory functions of rear extremities was observed after 112 ± 5 (mean ± SD) minutes in group L, 115 ± 2 minutes in the LT group and 115 ± 3 minutes in the LM group, tested by mild clamping stimulus on the hind limbs at 5-minute intervals. There was a total of 120 serum samples obtained. Determination of lidocaine serum concentration was not possible in eight (7%) samples (5 in L, 2 in LM and 1 in the LT group) due to matrix interferences. The estimated pharmacokinetic parameters are summarized in Table 1. In most animals (80%) a peak serum lidocaine concentration was detected ten minutes after epidural administration. There were no statistically significant differences in the detected serum lidocaine concentrations within observed groups of animals, or between males and females. The highest detected serum lidocaine concentrations ten minutes post epidural administration were found in group L. The highest concentrations 30 minutes post EA were found in the group LT. During the last two quantifications (60 and 90 minutes post EA) the highest serum lidocaine values were found in group LM. The trend of serum lidocaine concentration decline over the observed period of time did not significantly differ between the observed groups of animals, while differences in the values of the elimination half-life, especially in

the contrast to LM group, were evident. The serum lidocaine concentrations of most animals at 60 or 90 min after the EA decreased to at least 50% of the value of the first measurement.

Discussion

The analgesic efficacy of epidural administration of lidocaine, alone or in combination with tramadol or morphine, for orchiectomy in dogs was investigated by Almeida et al.[1]. This study concluded that the addition of tramadol to epidural lidocaine provides an efficient postoperative analgesic effect, comparable to that of a lidocaine-morphine combination. However, we have found no studies that provide data on the influence of tramadol or morphine on the absorption of lidocaine from the epidural space in dogs. Serum lidocaine concentrations after single epidural administration of lidocaine alone have been reported in dogs by Vnuk et al.[13]. In agreement with our results, maximum serum lidocaine concentrations in most animals occurred 10 minutes after epidural administration. Furthermore, this study's average serum lidocaine concentrations did not differ significantly from those in our study. There was a recent preliminary study published on the effect of adding morphine to epidural lidocaine on the absorption of lidocaine from the epidural space in rabbits[5]. In agreement with the results of our study, significant differences in lidocaine serum concentrations between those administered lidocaine alone and those administered a lidocaine-morphine combination were not observed. Actual serum lidocaine concentrations were significantly lower than those found in our study, which is understandable, given their use of a considerably smaller animal species in their study. To the best of our knowledge, the influence of tramadol on the resorption of lidocaine from the epidural space has not been previously reported. The results of our study suggest the addition of tramadol at a dose of 1.0 mg/kg will not cause significant changes in serum lidocaine concentration. Further studies are required to support these results. In consideration that lidocaine was used at recommended therapeutic doses, and the addition of morphine and tramadol did not significantly influence its absorption from the epidural space, signs of lidocaine toxicity were not observed in any animal during our investigation. Lemo et al.[9] reported muscle tremors as the first sign of lidocaine toxicity in dogs at 2.7 ± 1.1 μg/mL lidocaine serum concentrations. Values detected in some animals in the present study (Table) were even higher, but the total dose used was much lower (4 mg/kg) comparing to previous investigation. In research of Lemo et al.[9] a mean lidocaine dose 11.1 mg/kg was required before muscle tremors could be observed. Other researchers[15] reported much higher mean lidocaine serum concentration (8.21 ± 1.69 μg/mL) as toxic, where appearance of tonic muscular extension was considered as the earliest sign of lidocaine intoxication. The difference between reported toxic lidocaine concentrations could be explained by different criteria used to indicate the time when toxic effect began. Estimated pharmacokinetic values indicated prolonged elimination half-life of epidurally administered lidocaine with the addition of morphine, and shortened with the addition of tramadol, in contrast to its sole administration.

In conclusion, the results of present study indicate morphine and tramadol can be used as additives to epidural lidocaine in dogs at the investigated doses, without significantly influencing lidocaine absorption from the epidural space.

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